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THE CHANGES IN THE CIRCULATION IN AORTIC INSUFFICIENCY.

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(From the Department of Pathology, Columbia University, New York.)

In the case of lesions of the aortic valves, which cause them to be insufficient, there occur certain well known symptoms which are perhaps more characteristic than those following any other valvular lesion, and have been very minutely studied. Particularly striking are the collapsing pulse and the diastolic murmur with the hypertrophy of the heart, and especially of the left ventricle which follows. Ordinarily these things have been explained as being due to the regurgitation into the left ventricle of a portion of the blood thrown out at each systole, and this explanation has generally been regarded as satisfactory until recently when H. A. Stewart[1] in a study of this condition brought forward the problem as to the real cause of the fall of pressure therein and the significance of the position of the dicrotic notch in the pulse curve.

Of course when the heart has become hypertrophied, different conditions may prevail, and so, too, when other lesions of the heart or of the arteries exist, the simple impairment of the circulation resulting from the lesion of the aortic valves is obscured. It is necessary, therefore, to study the effects of aortic insufficiency produced in a normal animal, and this can easily be done, as in the work of Stewart, by tearing a segment of the valve with the valvulotome described in an earlier paper.[2]

[1] Stewart: Experimental and Clinical Investigations in Aortic Insufficiency. Arch. Int. M., January, 1908.

[2] MacCallum: Johns Hopkins Hosp. Bull., August, 1906.

Stewart confirmed the statement of Mackenzie, Broadbent and others that the dicrotic notch holds a position very low in the descending arm of the pulse wave, when there is aortic insufficiency, whereas it is normally above the middle of this slope. Since the dicrotic notch is normally found to be synchronous with the end of the systole, and since the dicrotic notch in aortic insufficiency occupies a position approaching the trough of the pulse wave, he concludes that the collapse occurs for the most part during the latter part of the systole. There can therefore be no regurgitation during that time and the collapse must be due to widening of the arteries and ready escape of the blood. A similar position is occupied by the dicrotic notch in the pulse of low arterial pressure. If the pressure is raised by compressing the aorta or by giving adrenalin, or, if from the existence of arteriosclerosis, the pressure is high, the dicrotic notch even in aortic insufficiency assumes a higher position and the pulse is no longer regarded as collapsing.

Further, since the diastolic arterial pressure is found to fall on the tearing of the aortic valve, while the systolic pressure is maintained, he argues that there must have been an attendant vasodilatation. Since the pulse pressure has been increased because of the fall in diastolic pressure, it can only have resulted from peripheral dilation.

Such a dilation of the peripheral vessels must constitute a protective adaptation which instantly comes into play upon

the tearing of the valve and must be brought about by vasomotor influences. Since this seemed at first sight hard to accept in place of the time honored explanation on the basis of regurgitation, I have examined it more closely. In order to approach these conditions I have devised an arrangement of the circulation, which I find, on looking over the literature, is somewhat like that used by Martin,[3] Howell and Donaldson,[4] excepting in that it does not interfere with the nervous connections of the heart, and is, on the whole, more manageable. I have also found the description of a somewhat similar device by Lohmann[5] in a recent journal.

It is as follows, the aim being to eliminate as far as possible the influence of the vasomotors and to determine directly the output of the aorta in relation to that of the ventricle. In devising a method which will give us the output of the heart under controlled conditions of peripheral pressure we must begin, I suppose, with the idea that such results may not correspond absolutely with those in the normal intact animal, but that when carefully measured before and after the insufficiency is produced, they will give us a clear idea of the changes which depend upon the insufficiency. This is all that one can claim for the results which follow, although as a matter of fact it seems perfectly easy to reproduce under such conditions a state of the circulation indistinguishable from that of the normal animal.

The method used will be made clear by the accompanying diagram (Fig. 1.) In order to eliminate the effect upon the heart of a peripheral resistance such as is offered by the systemic arteries, liable to constant change and difficult to measure and change at will, the aorta is cut through at the arch and connected with a canula and a long rubber tube with a curved glass outlet of the same caliber. This outlet can be set at any height upon the graduated vertical rods. A cistern supported at the same height and movable with the outflow nozzle, contains defibrinated blood usually mixed with Ringer's solution, which, after passing through a coil immersed in warm water, runs through a second canula into the distal portion of the aorta. Naturally, the first blood which escapes will clot and is not emptied into the cistern until it has been defibrinated; but after a short time all the blood in use has become defibrinated and the outflow nozzle may be turned so as to empty directly into the cistern. Then the circulation will go on indefinitely, differing from the normal in that it drops through the open air at one point and there may be caught and measured, and in that the variable peripheral arterial pressure is replaced by an outflow level which may be precisely controlled by merely moving the supporting clamp up and down on the graduated standard. Any necessary manometers may be attached laterally to the rubber tube which represents the aorta. A plethysmograph constructed after the manner of Henderson's but made in a more suitable shape, and of glass so that the heart can be seen, is put upon the heart and connected with a tambour whose movements have been calibrated. This plethysmograph is put into exactly that position in which it allows the heart to lie naturally and then fixed there with a clamped support. Its lower surface is made nearly flat so as not to dislodge the heart nor press upon the great veins.[6] The outflowing blood is caught in a graduated glass cylinder and as the level of the blood rises in the cylinder each 10 cc. is recorded by an electric signal writing on the same drum as the manometers and plethysmograph. All of these pens are exactly superposed.

The table, the height of which can be raised or lowered by a screw, is adjusted so that the heart is on a level with the zero of the graduated uprights which run nearly to the ceiling of the room. Pressure is then estimated in centimeters of blood although it is, of course, easy to read it off in millimeters of mercury from the curves. A Jacquet chronograph accompanies the manometers.

It is clear that a constant error is involved in estimating the total output, because although the subclavian arteries can be ligated, the carotids must be left open. Of course, one might arrange a separate circulation for the head, but the error is constant enough to make little difference in the result obtained. It involves a constant difference between the estimated value of the plethysmographic excursion and the measured output per beat. Part of this may be residual blood, but part is blood escaping into the carotids.

In introducing the canulas into the aorta it has been found advisable to open the subclavian artery and allow free bleeding while the aorta is clamped in order to relieve the strain upon the heart. When the animal is thus arranged, the pressure against which the heart expels blood into the aorta is determined by the position of the outflow tube. The pressure of the blood entering the distal portion of the aorta, and consequently the amount of blood finally supplied to the heart, depends upon the height at which the cistern is placed. If the cistern is maintained at a constant height and the outflow tube moved up and down, it is found that the actual output of the heart through the aorta is changed but little by the alterations in pressure, as pointed out by Howell and Donaldson. It seems, however, that when the cistern stands far above the outflow tube, a certain amount of blood must run through the animal to the outflow by the force of gravity.

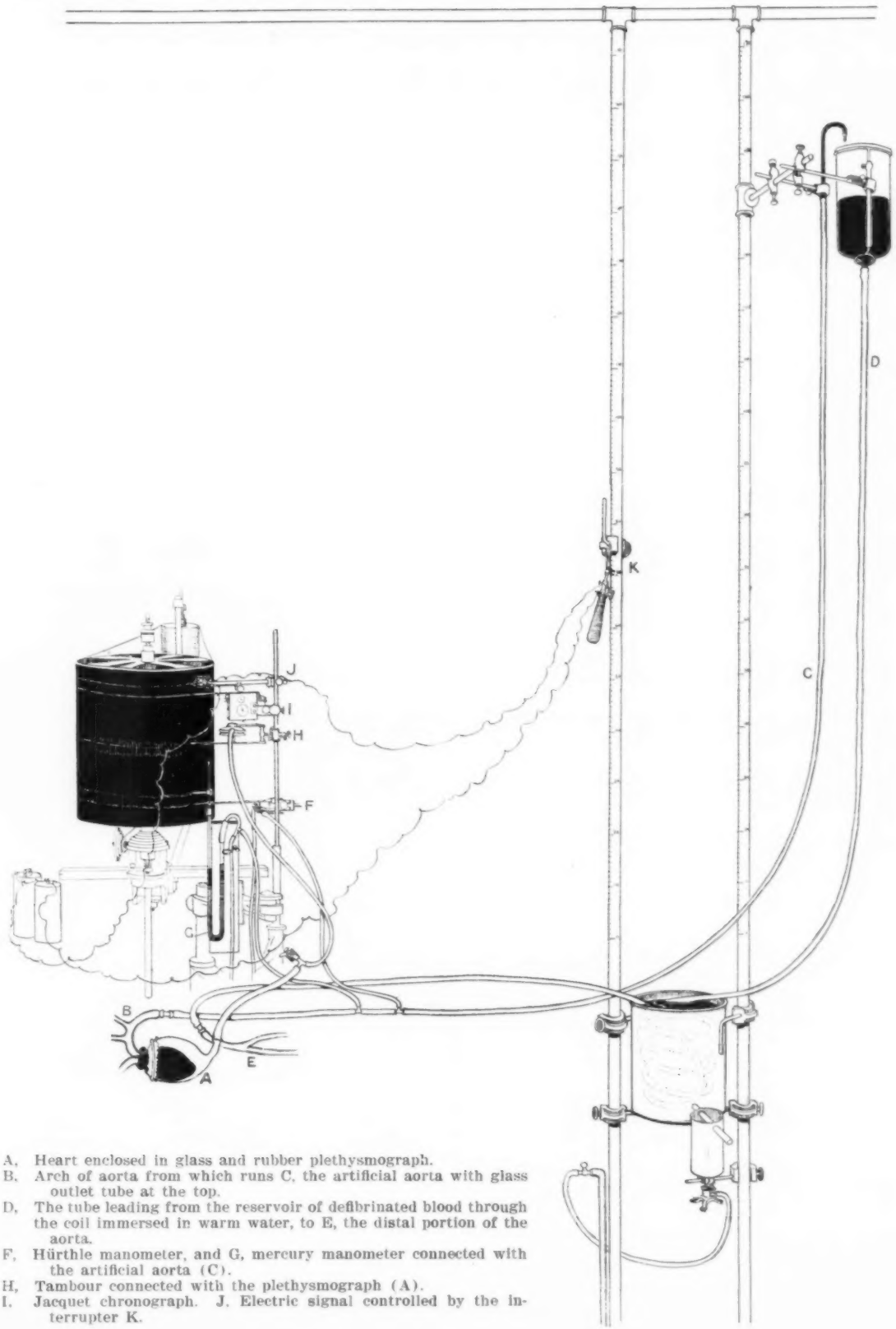
Ordinarily the elevation of pressure in the intact animal is produced by narrowing the arterioles which would undoubtedly tend to affect the amount of blood entering the veins; but apparently this is exactly compensated by the increased force and consequent rapidity with which the heart sends the blood through the narrow channels and the circulation proceeds as

[3] Martin: Philos. Trans. Roy. Soc., 1883, p. 663.

[4] Howell & Donaldson: Philos. Trans. Roy. Soc., 1884, part 1, p. 139.

[5] Lohmann: Pflüger's Archiv, 118, 1908.

[6] The tambour of the plethysmograph may be calibrated, of course, by attaching it to a flask into which a burette allows fluid to drop 1 cc. at a time, but it is much more readily and exactly done with a syringe. One cc. or 5 cc. of water is expelled from the syringe into a graduate and the ring on the piston rod then screwed down tight on the top of the syringe. After this the excursion of the piston is 1 cc. or 5 cc. as arranged and it is quite easy to communicate this to the tambour. It can be done rapidly and produces a curve like that obtained from the heart.



A, Heart enclosed in glass and rubber plethysmograph.
B, Arch of aorta from which runs C, the artificial aorta with glass outlet tube at the top.
D, The tube leading from the reservoir of defibrinated blood through the coil immersed in warm water, to E, the distal portion of the aorta.
F, Hürthle manometer, and G, mercury manometer connected with the artificial aorta (C).
H, Tambour connected with the plethysmograph (A).
I, Jacquet chronograph. J, Electric signal controlled by the interrupter K.

before. So, too, it is found that if the cistern and outflow tube are kept at the same level, the outflow and inflow are about constant and thus probably resemble more closely the conditions in the intact animal than when the inflow is kept constant and the level of outflow changed. Nevertheless, both conditions were studied in many curves.

When the level of the cistern and of the outflow were the same, the elevation of these increased the rate of the circulation. The amount of blood thrown out of the aorta per beat increases with the elevation; consequently, the amount of blood handled by the ventricle increases, the ventricle dilates and its excursion increases. It not only relaxes to a greater degree, but it contracts and empties itself completely. Thus the plethysmographic curve not only shows an increased excursion, with heightened pressure of this sort, but occupies a position further below the base line. This is the usual criterion of the tone of the ventricle, but if we disregard the conditions of malnutrition of the myocardium, of which we shall speak later, it seems that such accommodative dilatation, associated as it is with an improved excursion and the easy performance of increased work, should hardly be referred to as a diminution of tone. This, however, is a question of definition, and we hope to say more at another time of the question of tone. In practice, the plethysmograph was opened at each change of pressure so that its excursions, when again closed, were executed directly about the base line. In this way, calibration is less complicated and the disturbing element of the compression of the air in the plethysmograph was eliminated. When this was not done, however, it was found that at a pressure of 150-200 cm. of blood, the heart would make very great excursions at a level far below the base line, ejecting blood very rapidly, while at low pressures the heart became very small and made small excursions at a level far above the base line with relatively slight output of blood (Curve I). This seems to be chiefly dependent upon the amount of blood handled, for when the cistern was kept at a constant level, the excursions varied far less.

The character of the normal pulse may be studied in the curve of the Hürthle manometer taken from the aorta laterally. It might seem that the substitution of gravity for the resistance offered by friction in the arterioles might produce fallacies in the interpretation of the pulse curve, but after all, the elasticity of the arteries, represented here by that of the rubber tube, is the only force which forms the pulse aside from the peripheral resistance and the impulse from the heart. As a matter of fact, experiments were made to test this both in the normal intact animal and in those in which aortic insufficiency had already been produced, and it was found that the pulse curve, after the cutting of the aorta and the establishment of the new arrangement, was indistinguishable from that of the intact animal of five minutes before, as may be seen in the accompanying curves (Curve IX).

It might be thought that in the intact arterial tree it would be easy for the elastic contraction of the artery to continuously propel blood along into the veins, whereas in the upright rubber tube, the expulsion must depend upon the impulse of the heart alone; but a moment's reflection will show that with the cessation of the systolic impulse and the escape of blood over the level of the outflow, the level of the blood is still exactly there, and if the elastic tube is overdistended its recoil will drive more blood over, precisely as in the case of the arterial tree with its capillaries.

The pulse curve shows the dicrotic notch and wave precisely as in the intact animal. The position of this notch changes with changes in the level of the outflow, being low on the slope when the outflow is low and rising toward the summit of the primary wave, as the outflow tube, and consequently the pressure and tension of the wall are elevated.

It is difficult for me to believe that the form of the pulse wave can be directly dependent upon the rapid escape of the blood from the arteries. If the tube into which the heart ejects blood is elastic, and of any considerable length, even if it be widely open at its end, it will require an appreciable time for the blood to pass along and escape, and it seems probable that even in such a case the pulse wave will reach the end of the tube before the actual mass of fluid, the injection of which produced that pulse wave, does so and escapes.

Even if the elastic tube be of uniform caliber throughout, I do not believe that the form of the systolic pulse wave could be affected by the actual escape of the fluid, for it is certainly formed before that, if the tube is of any considerable length. To attain such a condition, the aorta would require to be like a very short, very widely open straight tube with rigid walls. Far less, then, does it seem possible that the arterial tree as it exists could afford such conditions even with the maximal conceivable dilation of the arterioles.

On the other hand, although it cannot be conceded that the systolic quantum of blood could get out of the way rapidly enough to produce a change in the form of that systolic wave (since the wave is an expression of pressure and not of the movement of fluid), it is obvious that its rapid removal will leave the vessel partly empty with relaxed walls when the time arrives for the next systolic impact; and it is this relaxed condition of the wall, I think, which causes the peculiar form of the pulse in aortic insufficiency.

Stewart has explained, on the basis of the work of Haycraft, Lewis, Roy and others, how the collapsing character of the pulse is dependent upon a low diastolic pressure, high systolic pressure and therefore high pulse pressure not being necessary. I may quote a paragraph: "From the figures given by Roy of the extensibility of the arterial walls at different pressures, two pulse curves are drawn (Fig. 35). In both instances the excess of systolic over diastolic pressure is the same, viz: 60 mm. Hg. but they differ in that in one the diastolic pressure is below normal, viz: 50 mm. Hg. while in the other it is somewhat above normal, viz: 80 mm. Hg. In the lower curve the amplitude is double that in the upper, the angle between the upstroke and downstroke is more acute, and the dicrotic notch relatively lower. In the upper curve, upstroke and downstroke are oblique and the angle between them is widened. In the curve taken at the low pressure there is more movement of the arterial wall for the same change of pressure. The one

would be classified as a "collapsing" pulse, the other as "sustained."

It seems that with low pressure the amplitude of the pulse is increased chiefly by the facile yielding of the lax wall of the incompletely distended artery so that the relative position of the dicrotic notch is due to the increased excursion of the vessel wall above that point in the curve at which the end of the systole is indicated by the dicrotic notch.

It can be readily shown that the actual amount of blood which escapes when the heart is working at a low pressure is less than that when the heart pumps against a high pressure because the amount supplied to the heart is less. In other words, the rate of the circulation becomes greater at the higher pressure, at least up to a certain optimum, but this seems to have nothing to do with the character of the pulse except in that, at the high pressure, the walls of the artery are under high tension while at a low pressure they are lax. At high tension the systolic pressure would not be able to expand the vessel so far by its sudden impulse before the closure of the valves and therefore the dicrotic notch would appear after only a slight systolic fling, whereas if the pressure during diastole is low and the walls of the vessel lax, the same systolic impulse

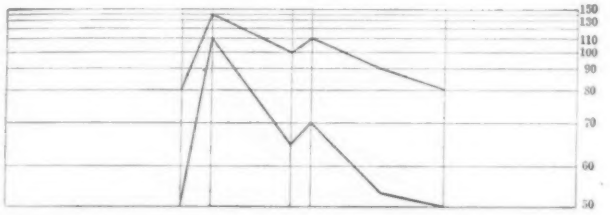


Fig. 35.—Diagrammatic representation of two pulse curves indicating the same pulse pressure, but at different diastolic pressures. The horizontal lines indicate the extensibility of the artery at given pressures (after Lewis).

would produce a considerable fling before the dicrotic notch which would therefore stand relatively low on the downward slope. Measured from the trough of the wave the dicrotic notch might stand equally high in a collapsing and a non-collapsing pulse, but in the collapsing, the excessive excursion above this would make the dicrotic notch relatively low. This is especially strikingly seen in the tremendous collapsing pulse which occurs when the heart is dying from inadequate coronary circulation. The slow but violent systoles throw a quantity of blood into the relaxed almost empty artery and a great fling results before the dicrotic notch.

This gives a ready explanation of the change in the character of the pulse when the aorta is compressed or adrenalin given. These measures increase the tension of the arterial wall by preventing the outflow and it is this increased tension which changes the form of the pulse. In the case of arteriosclerosis in which aortic insufficiency is said not to produce a typical collapsing pulse, it seems more probable that the rigidity of the artery wall prevents its being distended by the systolic impulse even more effectively than a heightened tension could. As a matter of fact while in the pulse curve of aortic insufficiency produced by tearing the valve the dicrotic notch may be quite high on the downstroke of the curve if the pressure is maintained at a fairly high level, it is often very indistinct and one receives the impression that the imperfection of the valves prevents its proper formation.

In the arrangement of the circulation described, the position of the outflow tube determines in a way the pressure. As long as the tube is full to the outflow level, that level represents the diastolic pressure. If the valves are intact the heart responds and maintains the level, but if its nutrition suffers, it dilates and the blood level falls rapidly in the tube. If the aortic valves are torn, the level is maintained but by more active work on the part of the heart. The systolic pressure rises above this, dilating the tube as shown by the summit of the pulse wave which passes along to the outflow.

If, in the animal with an artificial aorta, the outflow tube be set at any level and aortic insufficiency be produced, the pulse pressure instantly becomes greatly increased. There is nothing to represent the supposed accommodative widening of the peripheral vessels here and the outflow from the end of the tube per beat is practically always just what it was before, but still there is greatly increased pulse pressure both from systolic elevation and diastolic fall. The only possible explanation of this is the existence of regurgitation. This relaxes the tension of the wall of the vessel which then receives with the next systole the regurgitated blood together with the normal output. Since the amount of the regurgitated blood again sinks back, the actual outflow is the normal; but the impact of the whole mass thrown out by the heart on the relaxed arterial wall gives the collapsing character of the pulse wave, and the fall in the diastolic pressure must be due, not to a peripheral escape, but to an escape into the heart.

If the level of the outflow tube is high and a high systolic tension thus allowed, the systole will take place into a tube already tense—no great fling or sudden distension will be produced before the end of systole and the dicrotic notch will therefore be at the bottom of only a relatively small part of the downward slope. If the outflow tube be at a low level, less blood will reach the heart from the low cistern, less effort will be made to handle it, less will be thrown into the vessels whose size and elasticity are constant, and the lax wall will be given a fling which leaves the dicrotic notch low.

Another possible explanation of the position of the dicrotic wave lies in the fact that when the valves are torn they can hardly give rise to such a sharp wave or notch and that it may well be that the recoil is from the wall of the ventricle rather than from the valve. Indeed, in many of the curves of extreme insufficiency, it is difficult to discern anything of the dicrotic wave at all. This is especially suggested by the auscultation of the murmur, for although, of course, any such method must be inexact, one is much inpressed by watching the formation of the curve in a slowly beating heart with low dicrotic notch or hyperdicrotism following aortic insufficiency with the finger and the stethoscope on the heart. The murmur starts precisely with the end of the systolic heave and persists through the

downward slope to the trough or notch where it stops—the hyperdicrotic wave is executed in silence and then begins sharply the new systole (Curve VI).

On the whole, it seems that the position of the dicrotic notch is chiefly a question of the tension of the vessel wall. Similarly the collapsing quality of the pulse must be a question of the incomplete filling of the aorta just prior to systole and the consequent fling of its lax wall by the injection of the systolic quantum.

I can readily understand that long continuance of this condition might widen the arteries and thus possibly account for the capillary pulse which would be the more easily brought about by the impulsion of an excessive quantity of blood into the aorta even though that blood never reached the periphery. Indeed it is not hard to believe that with hypertrophy of the ventricle the blood might be sent more rapidly through the veins. *But all of these things are the final effects of the changes resulting from aortic insufficiency and not their causes.*

By means of the rearrangement of the circulation with the artificial aorta, it is possible to arrive at some mathematical conclusions as to the exact nature of the mechanism of the blood flow in aortic insufficiency, for it is easy to estimate the output from the aorta at each beat of the heart and at the same time to measure the output from the ventricle as calculated from the calibration of the plethysmographic tracing. When the valves are intact, these two figures are not far apart. A constant error lies in the escape of blood into the carotids, and nothing more than a comparison of the relations before and after insufficiency is attempted. When the valve is torn, it is found that the systolic pressure as shown by the manometers is maintained. The diastolic pressure sinks, the output per beat or at least per minute (for the rate may change and become slower) is about the same, the plethysmographic curve maintains its level or stands a little higher—its excursions are greatly increased in amplitude. These things are true of the artificial aorta and I find them true also of the animal with intact aorta, although Dr. Stewart finds no marked increase in the plethysmographic excursion. In a few experiments made to determine this point I have found an increased plethysmographic excursion exactly as in the cases with the aorta cut.

It must be borne in mind, however, that if there be regurgitation into the ventricle, the amount of blood actually circulating round to the heart will tend to be less than normal, while the volume of the left ventricle will be increased by the reception of the regurgitant blood. The volume of the right ventricle, will, however, be correspondingly decreased on account of the smaller amount of blood it receives. Such a combination might conceivably proceed without on the whole any enlargement of the heart and in that way account for the high level of the plethysmographic curve.

Before the insufficiency, the amount expelled per beat from the aorta nearly equals that put out by the ventricle, but immediately upon tearing the valve there arises a great discrepancy. The excursion of the cardiac plethysmograph becomes much greater, showing a much larger output, while the aortic delivery remains practically unchanged—undoubtedly therefore, at each beat a considerable quantity of blood is thrown out of the heart into the aorta which never reaches the outflow orifice. It must go back into the heart and be thrown out again in the same futile way at the next systole. Even at such low pressures as 30 mm. Hg. this "residual" blood may be three times as much after the lesion as it was in the normal heart at pressures of 60 or even 100 mm. Hg.

There is thus a considerable regurgitation, and when a regurgitation of 1 or 2 cc. is spoken of in a dog it is by no means insignificant, for repeated studies of the output per beat at normal pressures in dogs show that quantities such as 10-12 cc. per beat are far too great and that the dog's heart actually puts out quantities nearer 2 cc. per beat when the dog weighs 7 or 8 kg.

The estimation of the work of the heart at any given level of aortic pressure as the product of the plethysmographic excursion and the rate shows us that there is a sudden great increase when the aortic valve is cut. Thus, in one experiment in which the pressure in the aorta was 120 cm. of blood, the work of the ventricle per minute was represented by 348.4 cc. of blood as compared with 220.9 cc. before the valve was torn, although the actual output from the aorta during this time was only 228 as compared with 203 while the heart was intact. This difference is evidently to be accounted for entirely by the regurgitation of the blood and the hypertrophy of the ventricle is, in the same way, easily accounted for as the result of the excessive amount of useless work put upon the ventricle by the imperfection of that mechanism which normally secures and renders permanent the effect of each contraction.

Positive efforts to make clear the nature of the collapsing pulse may easily be made with this modified arrangement of the circulation. It seemed possible that the mere excess of blood from whatever source which the ventricle was called upon to handle, might stimulate its walls to more violent contractions and thus heighten the pulse pressure. To test this, blood was led from another cistern at a rather higher pressure into the left ventricle through a glass tube which was introduced in one instance through the subclavian artery and between the aortic valves in a heart in which no valve had been torn, and in another experiment on a normal dog the extra blood was brought into the ventricle through the same sort of tube which was introduced through the auricular appendix and the mitral orifice into the ventricle. In both cases the valves closed snugly about this tube and there was no leakage. In both experiments the result was merely a slight elevation of pressure and a considerable increase in the aortic output (largely due, no doubt, to gravity). Nothing of the collapsing character appeared in the pulse.

On the other hand, when the tube passing into the left ventricle was led, not from a separate blood reservoir at a high level, but from any point along the side of the artificial aorta which was tapped with the aid of a "T" tube, the pulse instantly assumed the collapsing character when the artificial regurgitation was allowed, and as suddenly stopped and returned to normal when that tube was clamped. Undoubtedly

this experiment reproduces in the normal heart the principle of regurgitation which is shown in the heart with a torn aortic valve. In this curve the height of the dicrotic notch will correspond roughly with the level at which the aorta is tapped.

Again, if in an experiment in which a collapsing pulse has been produced by tearing the valve, we introduce an artificial valve into the tube which represents the aorta, the pulse will lose its collapsing character, and the more perfectly the valve acts the more nearly will it approach the normal form.

From all this it seems unavoidable to conclude that regurgitation plays a predominant part in the whole complex of aortic insufficiency. The ventricle throws out a quantity of blood into the aorta, which is more than naturally emptied and relaxed by the regurgitation of the previous diastole, thus giving a great fling to the loose wall. Much of the blood returns to the ventricle being in fact only churned out and back from the ventricle. Still, so great is the new effort that a normal or nearly normal amount of blood may be discharged from the aorta. The great pulse pressure produced in this way is very characteristic and since it persists at all pressures it would seem to constitute a specially good criterion of the condition. The dilatation of the peripheral capillaries at each pulsation must be due to the same projectile form of systolic filling of the relaxed vessels.

CONCLUSIONS.

1. By means of the arrangement of the circulation described, it is possible to estimate the work of the ventricle and to study the influence of various factors upon it.

2. The tearing of an aortic valve producing an aortic insufficiency causes the heart to perform an extraordinary amount of work, part of which is devoted to the maintenance of nearly a normal rate of flow on the vessels, while the remainder is expended upon the forcing out of a quantity of blood which each time regurgitates through the torn valve.

3. This extensive and violent excursion of the ventricle together with the effect of the regurgitation produces a very great pulse pressure with low diastolic pressure and the low tension of the arterial wall allows a great systolic fling which occupies a relatively large part of the height of the pulse curve and thus causes the dicrotic notch to occupy a low position which is another characteristic of the collapsing pulse.

The following protocols will show the character of the results obtained by measurements and may be compared with the corresponding curves in so far as they are reproduced. It must be emphasized that the figures have practically no absolute value. An approximate idea of the output of the aorta at varying pressures is obtained but there are many sources of error. So, too, the results obtained by calculation from the calibration of the excursions of the plethysmograph seem to me of very doubtful absolute value. It is possible to change the excursion so greatly by the slightest movement of the plethysmograph or by the slightest inaccuracy of the adaptation of the rubber to the auriculo-ventricular sinus that any arbitrary uniform calibration would seem to me as valuable as the particular factor which is found by calibrating the tambour. Although this is so, when the plethysmograph is once fixed immovably in place the relative values before and after the valvular lesion is produced are perfectly trustworthy, and although as absolute figures they may mean nothing, they give a perfectly good indication of the changes which ensue upon the tearing of the valve. In considering these figures allowance should have been made also for the fact that under such abnormal conditions the size of the two ventricles does not vary equally, so that while in the normal heart an increased flow of blood into the heart might mean an equal enlargement of the ventricles, such an effect might be modified in the heart with torn aortic valve, by the fact that an increased regurgitation would cause a disproportionate enlargement of the left ventricle. This would accentuate the modifications of the "residual blood" which are given in the protocols in which no such allowance is made.

Further, it will be seen that the malnutrition of the heart muscle which follows the severer insufficiencies, may be enough to cause the rapid dilatation of the heart and the death of the animal. In such cases the results are quite different from those in which the heart maintains its activities and one of them is given as an illustration (Table IV). Another (Table III) shows a milder degree of the same thing as the curve progresses and shows also the compensation that may take place when the lesion is merely a hole in the valve by the filling of the hole with clot.

The principles outlined in the above discussion are, however, shown to be true in all the curves if allowances be made for the disturbing effects of malnutrition of the heart muscle.

TABLE I.—February 23, 1911. Normal dog. Wt. 10 kg.

Peripheral pressures	70 cm.	150 cm.	150 cm.	150 cm.	70 cm.
Pleth. swing	18.75	24.	27.5	31.	15.
Calibration	.158+2	.070=1	mm.		
Estimate	1.48	1.896	2.172	2.449	1.185
Pulse rate	180	225	240	240	220
No. of beats to give 10 cc	10.3	5.87	5.5	6.5	10.5
One beat gives	.97	1.703	1.818	1.538	.952
Residual blood	0.51	.193	.354	.911	.233
Aortic output per minute	174.6	382.5	436.3	369.12	209.4
Heart work per min. (Pleth. x rate)	266.4	526.6	521.2	587.7	260.7

The table shows the changes in the work done by a normal heart with changes in outflow and inflow pressure.

TABLE IV.—January 3. Dog, weight 8.7 kg. Inflow and outflow at 62 cm. Extreme injury, death from dilation.

	Normal.	Aortic insufficiency.
Pleth. swing	12	15
Calibration	.158=1 mm.	divide by 2=.079
Estimate	.948	1.185
Pulse rate	170	120
No. of beats to give 10 cc	17	22.7
One beat gives	.588	.440
Residual blood	.360	.745
Aortic output per minute	100.	89.4
Heart's work per min. (pleth. x rate)	161.16	142.2

TABLE II.—December 23. Outflow 57 cm., inflow 75 cm.

	A	B	C	D	E	F	G	H	I
Plethysmographic swing	12.	26.5	31	35	35	33	32		
Calibration	1 mm = 0.1584 cc.		Each result is divided by 2 for left ventricle.						
Estimate	.9504	2.0988	2.455	2.772	2.772	2.613	2.534		
Pulse rate	240.	120	90	90	95	95	110	120	120
No. of beats to give 10 cc	23.4	10.6	7	6.65	7.46	7.4	8	15.85	16.8
One beat gives	.427	.943	1.428	1.504	1.340	1.351	1.25	.63	59
Residual blood	.623	1.155	1.027	1.268	1.432	1.262	1.284		
Aortic output per minute (rate x beat value)	102.48	113.16	128.52	135.36	127.30	128.34	137.50	69.3	70.8
Heart work done per minute (pleth. x rate)	228.	251.8	220.9	249.4	263.3	248.2	278.7		

The table shows the effect of the production of aortic insufficiency just before B.

TABLE III.—January 19, 1911. Dog, weight 10.8 kg. Inflow 80 cm., outflow 60 cm.

	Valve cut.							Valve cut again.					
	1	2	4	5	6	7	A	B	D	F	G	H	I
Plethysmographic swing	17	24	29	26	24	24	26	27	29.5	34	30	33	32
Calibration		1 mm. = .158 cc.		All results divided by 2.									
Estimate	1.343	1.896	2.291	1.975	1.896	1.896	1.975	2.133	2.33	2.686	3.008	2.607	2.528
Pulse rate	190	160	175	175	175	175	170	165	165	170	160	160	160
No. of beats to give 10 cc	25	16	12.8	17.3	21.5	21.5	8	8.2	7.9	8.2	8.6		
One beat gives	.4	.625	.78	.578	.464	.464	1.25	1.219	1.265	1.219	1.515	1.33	1.33
Residual blood	.943	1.271	1.511	1.397	1.432	1.432	.725	.914	1.065	1.467	1.565	1.277	1.198
Aortic output per minute	76.0	100	134.50	101.15	81.2	81.2	212.5	201.13	208.72	207.2	242.4	252.70	
Heart output (pleth. x rate)	255.1	303	400.9	345.6	331.8	331.8	335.7	351.9	384.4	456.6	492.8	495.8	485.3

In this experiment the inflow pressure was higher than the outflow and was not changed. Insufficiency was slight in the first curve, the parts of which are numbered. In the second curve the heart had gained in vigor and a further tear of the valve was produced between B and D. Apparently the regurgitation was nowhere very great.

TABLE V.—January 11. Dog, weight 11.8 kg. Pressure 60 cm.

	Normal.	Aortic insufficiency.
Pleth. swing	15	25
Calibration	1 mm. = .079	
Estimate	1.185	1.975
Pulse rate	160	130
No. of beats to give 10 cc	19.8	19.7
One beat gives	0.505	0.507
Residual blood	.680	1.468
Heart's work per min. (pleth. x rate)	189.6	256.75

TABLE VI.—March 14, 1911. Weight 6 kg.

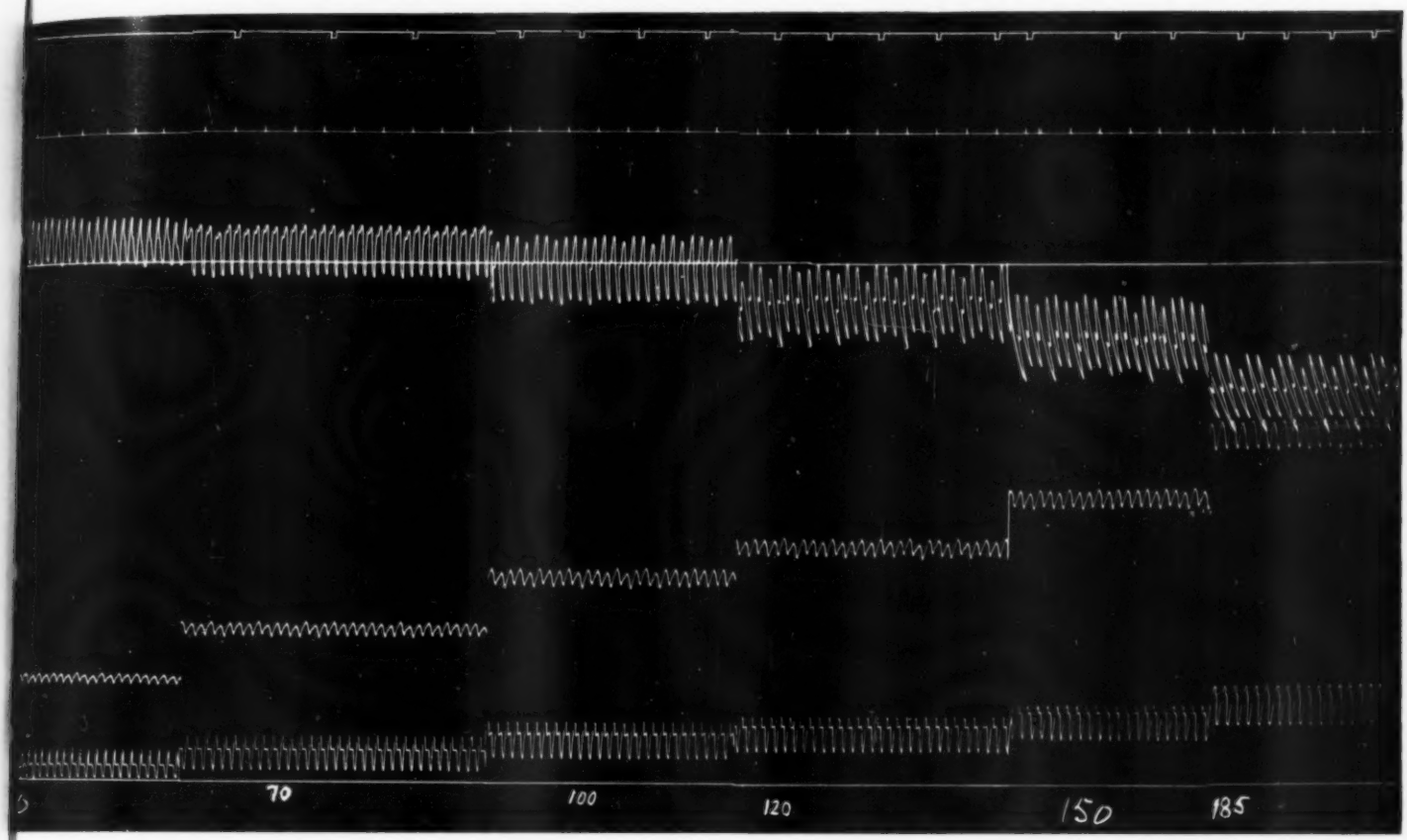
	Normal.		Aortic Insufficiency.				
	A	B	C	D	E	F	G
Periph. pressure	80	120	120	70	40	150	150
Pleth. swing	14.3	18	27.5	16.24	13.26	29.6	37.7
Calibration	1 mm.	=.01584	All results divided by 2.				
Estimate	1.1297	1.4259	2.178	1.286	1.05	2.344	2.9858
Pulse rate	150	155	160	180	160	160	160
No. of beats to give 10 cc	10	7.6	7	11	16	5.5	5.5
One beat gives	1	1.316	1.4285	0.909	0.625	1.818	1.818
Residual blood	.1297	.1096	.7495	.377	.325	.526	1.1678
Aortic output per min.	150	203	228	163	100	290.8	290.8
Cardiac output per min. (pleth. x rate)	169.4	220.9	348.4	231.48	223	875	477.7

TABLE VII. April 24. Dog, wt. 7.6 kg. Small aperture pierced in valve.

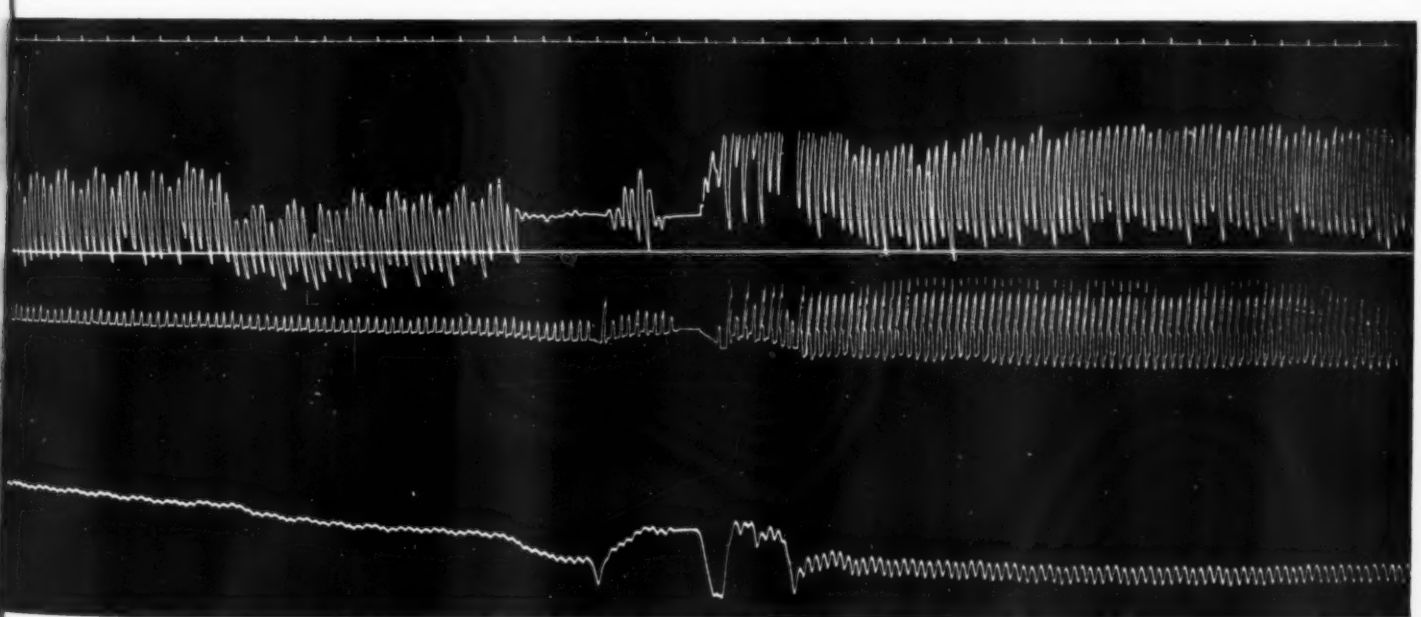
		Valve cut.		
Pressures	100	120	120	100
Pleth. swing	20.1	27	28.16	24.8
Calibration		5 cc. = 35 mm.		
Estimate	28.7	38.5	40.2	32.57
Pulse rate	200	195	190	195
Number of beats to give 10 cc.	7	5.8	5.7	6.5
One beat gives	1.42	1.72	1.75	1.53
Residual blood	1.45	2.13	2.27	1.727
Aortic output per minute.	284	335.4	332.5	298.3
Heart output per minute (pleth. x rate)	574	760.7	763.8	636.1

TABLE VIII. April 24, 1911. Dog, weight 9.4 kg.

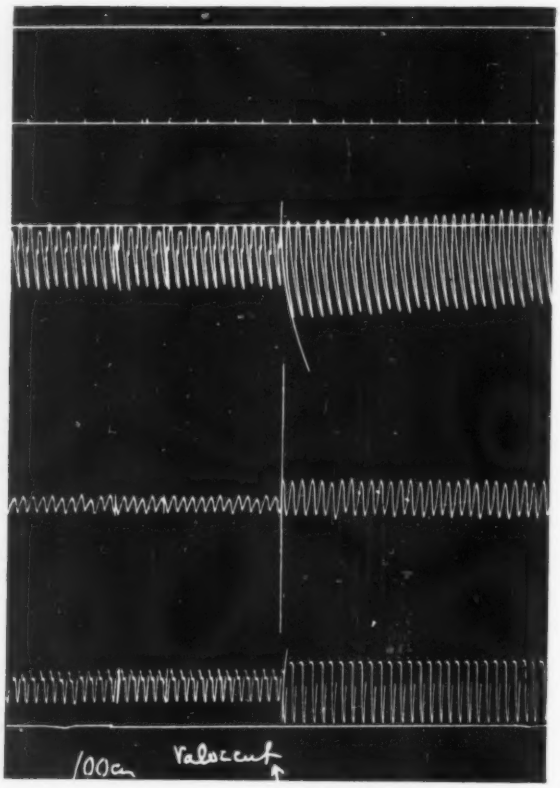
		Aortic valve cut.		
Pressures	100	120	120	100
Pleth. swing	10.3	13.66	20.9 (17.46)	18.2
Calibration		35 mm. = 5 cc.		
Estimate	1.47	1.95	2.98 (2.49)	2.6
Pulse rate	250	250	250	240
Number of beats per 10 cc.	8.26	7.5	7.3 (7.8)	8.57
One beat gives	1.21	1.33	1.37 (1.28)	1.166
Residual blood	0.26	0.62	1.61 (1.21)	1.434
Aortic output per minute.	302.50	332.50	342.50	279.84
Heart output per minute. (pleth. x rate)	367	487.5	745	624



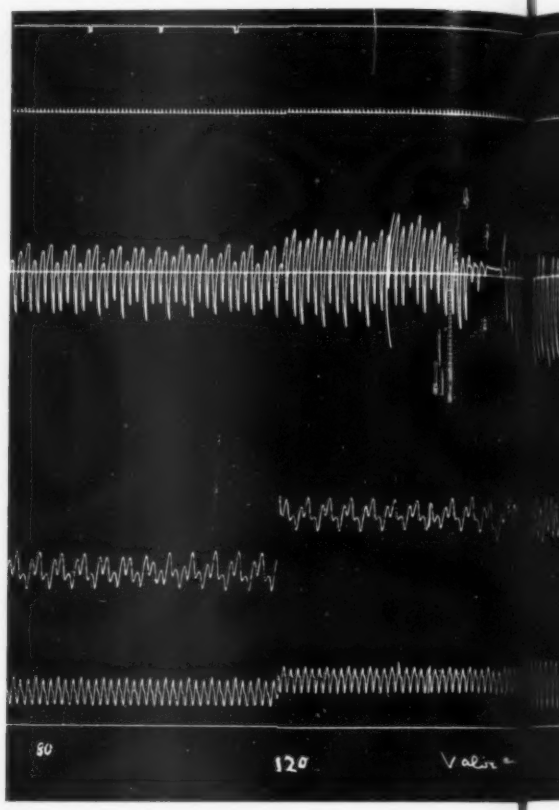
URVE I.—March 30. Dog weight 9 kg. The curve shows the changes in the position of the dicrotic notch, upon the Hürthle tracing and the ension of the heart with increasing inflow of blood. The excursion of the heart is also seen to be greater at the higher pressure.



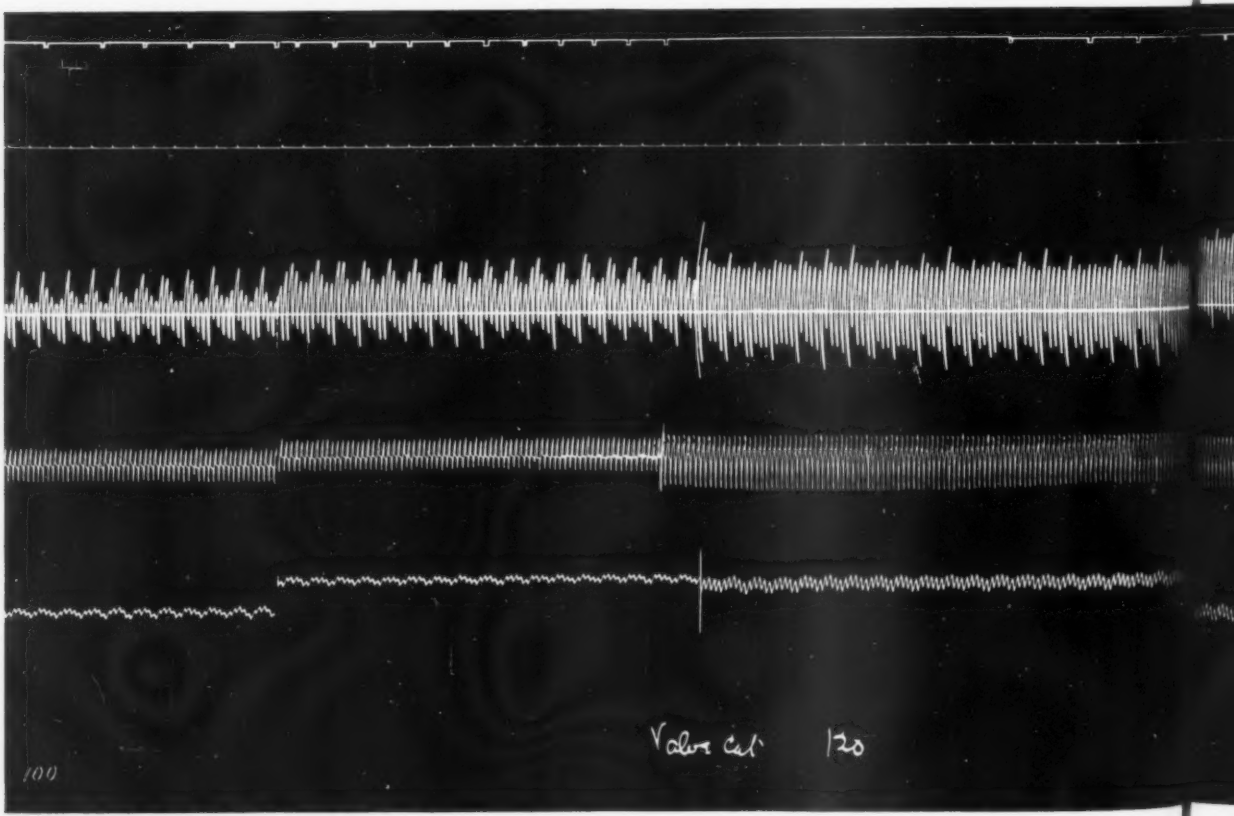
URVE II.—May 7th. Dog weight 7.2 kg. Plethysmographic and other tracings from dog with intact aorta, and after the tearing of the aortic valve. plethysmographic excursion is increased and the increased pulse pressure is characteristically shown in the curve from the Hürthle manometer.



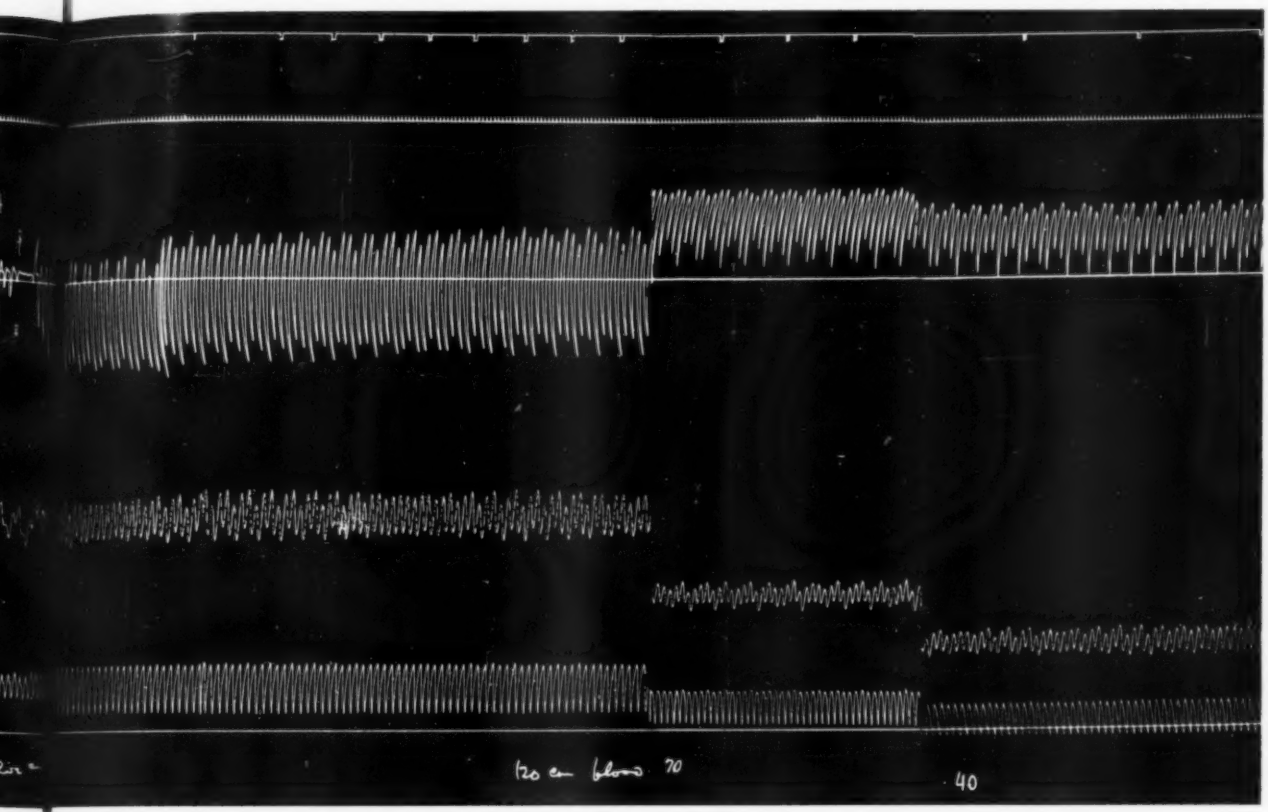
CURVE III.—March 30. Dog weight 9 kg. Characteristic change in all curves on tearing of the aortic valve.



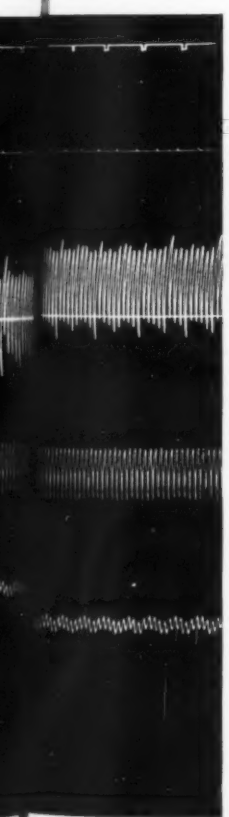
CURVE IV.—March [illegible] outflow



CURVE V.—April 24. Dog weight 9.4 kg. Curves at pressures of 100 and 120 cm. of blood, before and after cutting valve.



March 1 utflow and inflow pressures of 80, 120, 70 and 40 cm., before and after cutting of aortic valve.



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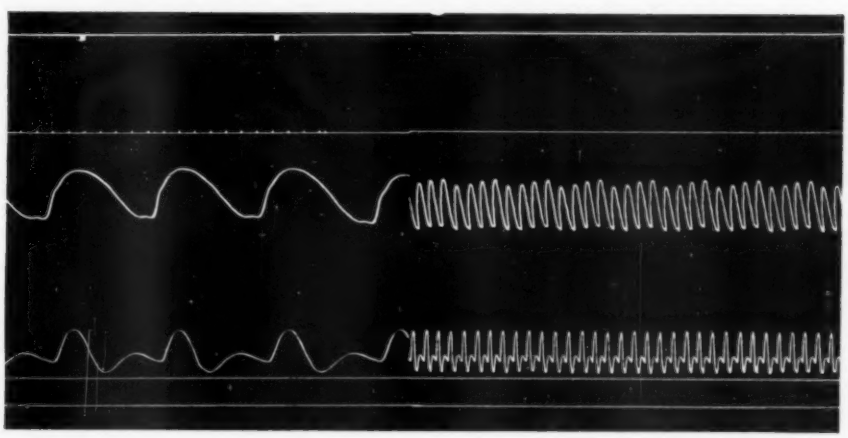
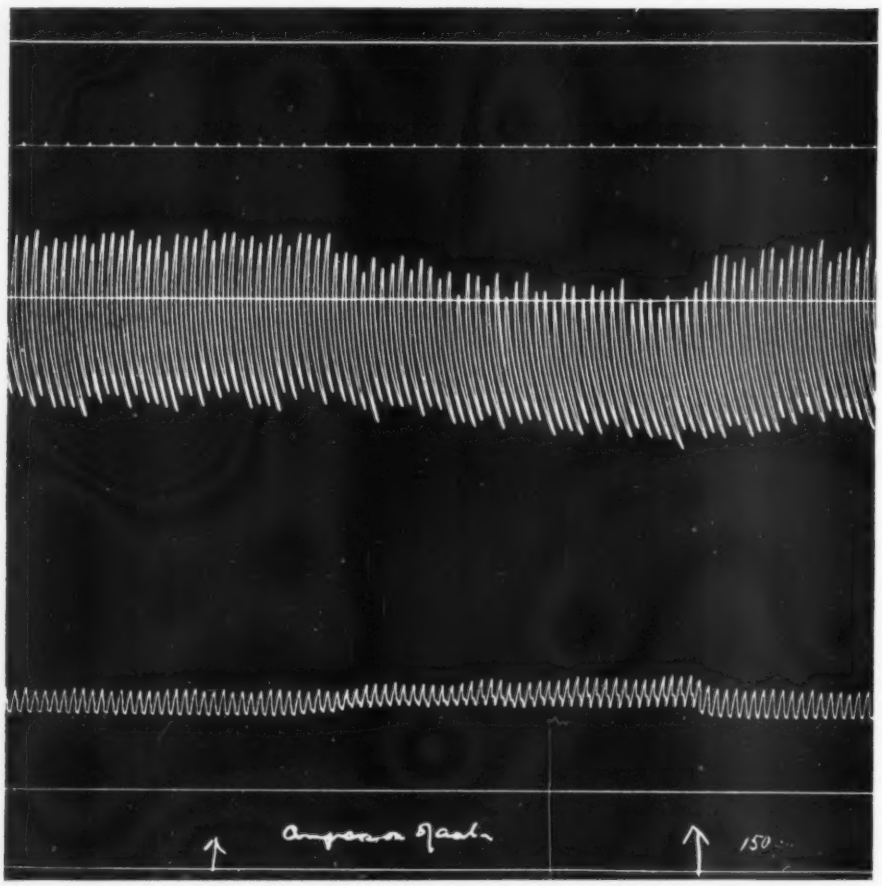
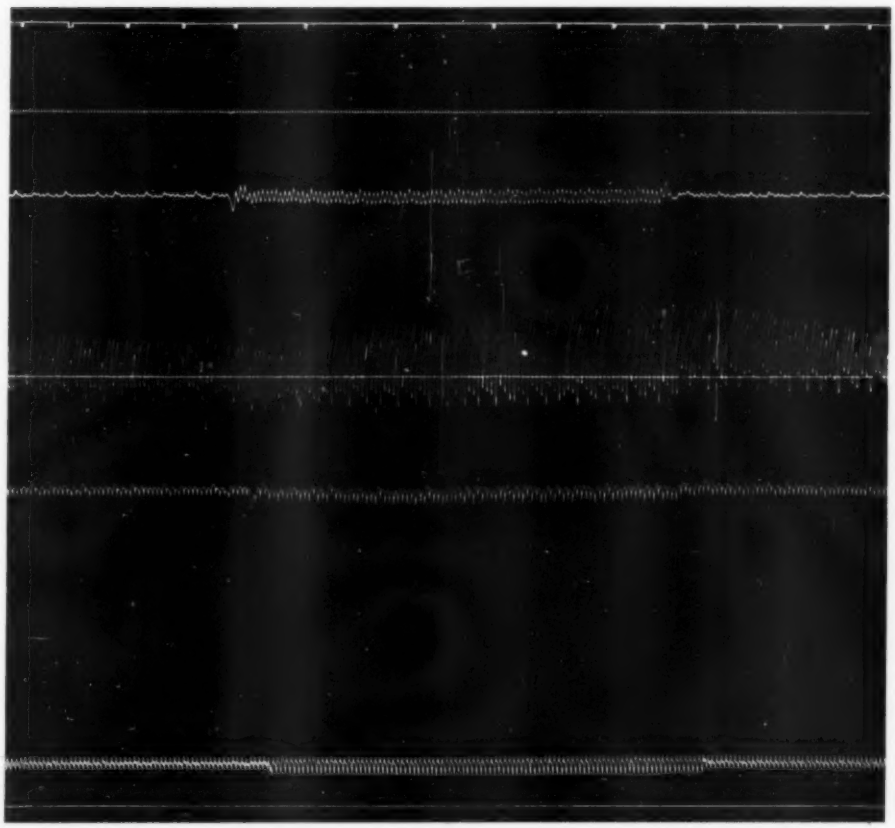


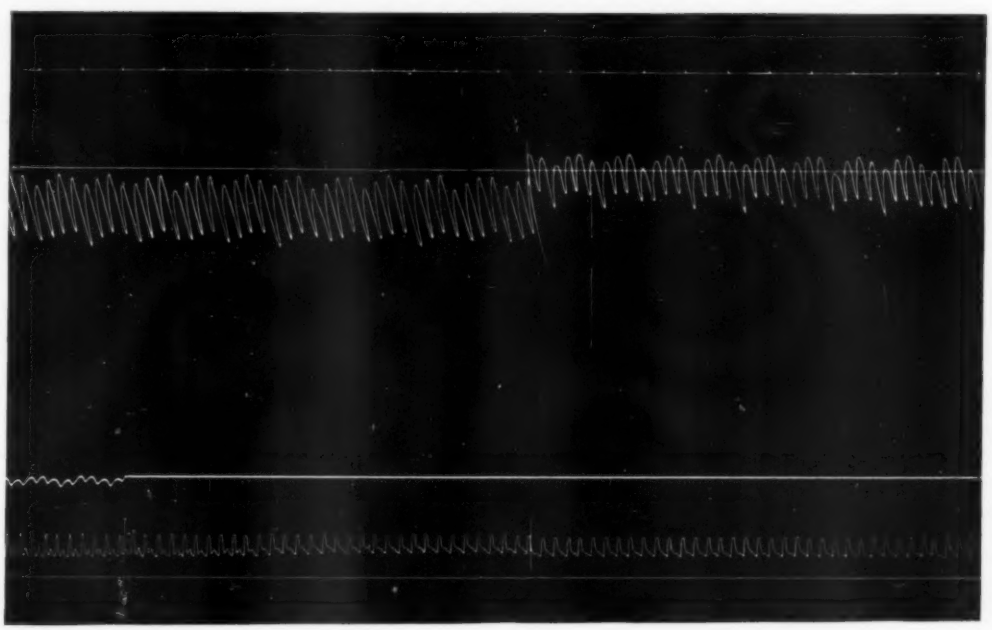
CURVE VI.—April 17. Plethysmographic and Hürthle curves in aortic insufficiency in the curve which has become hyperdicrotic. It was in this curve that auscultation showed the part of the curve occupied by the murmur.



CURVE VII.—April 6. Dog weight 6.3 kg. Curve shows the accentuation and elevation on the slope, of the dicrotic notch on compression of the aorta.



CURVE VIII.—February 7. The curve shows the appearance of a collapsing pulse produced by allowing regurgitation from the artificial aorta by tapping it with a "T" tube as described in the text. It is observed that the output is decreased during this regurgitation. Other particulars are mentioned in the text.



CURVE IX.—Shows absence of alteration of character of pulse on introducing artificial arrangement of circulation. It also shows that the fling of the mercury manometer has no influence upon the Hürthle record.

A FURTHER NOTE ON THE CLINICAL USE OF SCARLET RED AND ITS COMPONENT AMIDOAZOTOLUOL, IN STIMULATING THE EPITHELIATION OF GRANULATING SURFACES.*

By JOHN STAIGE DAVIS, M. D.,

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INTRODUCTION.—In a paper published in THE JOHNS HOPKINS HOSPITAL BULLETIN, in June, 1909, I reported the results of my observations during the treatment of 60 cases with scarlet red in various combinations.

Since that time I have been impressed by the great interest in the clinical use of this dyestuff as shown by the large number of papers on this subject which have appeared in the foreign journals, and also by a number of personal communications reporting favorable results.

The object of this article is to bring the subject up to date as far as possible, and in addition to make a few observations on the clinical use of amidoazotoluol, which was first tried by Hayward† and is a component of the scarlet red originally used by Fischer.

I was very skeptical when I began to experiment with scarlet red. It was difficult to believe that by the application of a commercial dyestuff such rapid epithelial stimulation could take place in sluggish wounds, some of which had been unhealed for many years.

It has been suggested that possibly the wounds healed with scarlet red were in a period of development in which, after being inactive for a longer or shorter time, the rapid epithelial growth would have taken place just as well under any other method of dressing. This may be true in a few instances, but I hardly believe it could have been the case in the large number of cases reported, where the process of healing had been at a standstill until this dressing was begun.

Carrel, in his very interesting article on "The Treatment of Wounds" (J. Am. M. Ass., 1910, p. 2148), says that when at the end of the period of "granulous retraction" of a large wound the edges of the old epidermis are still at a distance of 20-25 mm., the new epidermis cannot spread on the granulations and the cicatrization of the wound comes to a standstill.

Now, in practically all of the wounds which I have treated with scarlet red and amidoazotoluol, the period of "granulous retraction" had long since ceased, the period of epidermization had also come to a standstill, and the areas were, for the most part, very large. In spite of these facts, in the large majority of cases there was marked epithelial stimulation from the hitherto sluggish edges following the application of the dyestuff, and subsequent rapid healing.

Scarlet red was used exclusively as a dye until 1900, when Michaelis found that this coloring matter was very suitable for staining fat in the cellular tissue for microscopic examination.

EXPERIMENTAL USE.—B. Fischer in 1906, in a paper on the "Experimental Generation of Atypical Epithelial Proliferation," produced by the subcutaneous injection of a saturated solution of scarlet red, in olive oil, in a rabbit's ear, first called attention to the remarkable stimulating properties of this dyestuff, and suggested that therapeutic advantage might be taken of it. Since his publication a number of investigators (Ritter, Jores, Geipel, Snow, Stahr, Wyss, Helmholz, McConnell, Seckel, Hertzler, Schreiber and Wengler, Werner, Enroth, Stoeber, Grimani, Dixon, Cords, Wessley, Meyer, Borst), following Fischer's lead, have repeated his experiments and extended them. As far as I can ascertain, all, with the exception of Snow, have agreed that a new growth of epithelium is produced.

Several kinds of animals have been used, rabbits, Belgian hares, guinea pigs, white rats, mice, monkeys, dogs, cats, etc. These proliferations have also been produced in man. Wessley experimented on himself, and Stoeber upon a man 80 years old, whose leg was to be amputated for ununited fracture. The results were not as marked as in the rabbit's ear, on account of anatomical conditions, but were definitely positive. Stoeber injected scarlet red, amidoazotoluol and alpha naphthylamin, but did not succeed in producing epithelial proliferation by alpha naphthylamin. It is beyond the scope of this paper to discuss the theories as to the cause and source of these atypical epithelial proliferations.

An interesting point is made by Claribel Cone, who says that in the epidermis of man the fat which is shown by the scarlet red stain is especially noted in the basal (germinal) layer at the point of contact of the cell body and nucleus; in other words that the scarlet red attacks the living cell just at the point where physiological cell changes are most active. She suggests that this may cause a chemical or physical stimulation of the cell, and thus account for the active proliferation following its clinical use.

CHEMISTRY.—In looking over the literature on the clinical and experimental use of scarlet red I find that there are several chemically different dyestuffs which are marketed under the name scarlet red. I will consider the chemical formulæ of four of these.

(1) The dye used in my series in 1909 was the sodium salt of diazo-azo-benzene-disulphonic acid Beta naphthol.

Commercial Names.—Biebrich Scarlet; Pouceau 3 RB; Pouceau B; Fast Pouceau B; New Red L; Imperial Scarlet (Schultz & Julius, 1904, p. 110, No. 163).

* Read before the Johns Hopkins Hospital Medical Society, April 3, 1911.

† All references are arranged alphabetically under "Bibliography" at end of this article, so that the papers referred to under authors' names are readily to be found.

$$C_6H_4 \begin{matrix} \diagup \\ \diagdown \end{matrix} \begin{matrix} So_3Na. \\ N=N-C_6H_3-N=N-C_{10}H_6OH \end{matrix} \quad \begin{matrix} So_3Na. \\ \diagup \\ \text{(Beta)} \end{matrix}$$

Method of Preparation.—Amido-azo-benzene-disulphonic acid and Beta naphthol. It is a red powder, soluble in water and slightly soluble in alcohol. Insoluble in ether.

(2) Benzene-azo-benzene-azo Beta naphthol.

Commercial Names.—Soudan III; Cerasine Red (Schultz & Julius, 1904, p. 106, No. 143).

$$C_6H_5-N=N-C_6H_4-N=N-C_{10}H_6OH \quad \text{(Beta)}$$

Method of Preparation.—Amido-azo-benzene and Beta naphthol. It is a brown powder, soluble in alcohol and fats. Insoluble in water.

(3) Toluene-azotoluene-azo Beta naphthol. This is the scarlet red originally used by Fischer and Schmieden.

Commercial Names.—Oil Scarlet; Red B Oil Soluble Extra-concentrated; Pouceau 3 B (Schultz & Julius, 1904, p. 108, No. 150).

$$\begin{matrix} CH_3 \\ \diagup \\ C_6H_4-N=N-C_6H_3- \end{matrix} \begin{matrix} CH_3 \\ \diagup \\ N=N-C_{10}H_6OH. \end{matrix}$$

Method of Preparation.—Amido-azo-ortho-toluene and Beta naphthol. It is a dark reddish-brown powder which cakes at about 175° C. and melts at 184° to 186° C. Insoluble in water, soluble in alcohol and chloroform, fats, fatty oils, and also warmed vaseline and paraffine.

(4) Sodium salt of xylene-azo Beta naphthol monosulphonic acid.

Commercial Names.—Scarlet G. R; Scarlet R; Brilliant Orange R; Orange L (Schultz & Julius, 1904, p. 86, No. 54).

$$\begin{matrix} (CH_3)_2 \\ \diagup \\ C_6H_3-N=N-C_{10}H_5- \end{matrix} \begin{matrix} OH. \\ \diagup \\ So_3Na. \end{matrix}$$

Method of Preparation.—Xylidene and Beta naphthol monosulphonic acid. It is a cinnibar red powder, soluble in water.

I have used clinically the first three of these preparations with success, and also xylidene scarlet (Schultz & Julius, 1904, p. 96, No. 55) which is closely related to the fourth preparation. I find the best and most consistent results with scarlet red have followed the use of the dyestuff originally employed by Fischer and Schmieden. Hayward says that in the few cases reported where no result was attained this special dye was probably not used. He has also experimented with Soudan I, Soudan IV and Soudan G, with more or less success.

He says that Fischer and Schmieden thought that Alpha naphthylamin caused the epithelial stimulation in the most far-reaching way. Hayward used this substance clinically, and found that it caused only marked irritation. This was also my experience when I used Beta naphthol ointment of a strength corresponding to that actually entering into the formation of 8 per cent scarlet red, i. e., 2.4 per cent.

Experimenting further Hayward employed amidoazotoluol, the other component of scarlet red, and found that this substance caused a more marked stimulating effect on the growth of epithelium than did the scarlet red.

$$\begin{matrix} CH_3 \\ \diagup \\ C_6H_4-N=N-C_6H_3- \end{matrix} \begin{matrix} CH_3 \\ \diagup \\ NH_2. \end{matrix}$$

Method of Preparation.—Slowly add a saturated solution of sodium nitrate (1 mol.) to a mixture of orthotoluidine (4 mols.) and concentrated hyrochloric acid (2 mols.) and keep at a temperature of 30° to 40°. It is a reddish-brown granular powder. Melting point about 100° C. Nearly insoluble in water, but easily soluble in alcohol and ether.

CLINICAL USE.—A few words concerning the papers which have appeared on the clinical use of these substances may be of interest.

Schmieden was the first to follow Fischer's suggestion that scarlet red be used therapeutically, and in February, 1908, published a paper on his clinical results, which were very favorable. He reported rapid healing of sluggish ulcers of various kinds and in different situations. He used 8 per cent ointment and alternated the dressing every 24 hours with some bland ointment on account of the irritating properties of the scarlet red. He also used with success adhesive plaster impregnated with 10 per cent scarlet red for strapping leg ulcers.

He insisted that the granulations must be perfectly clean and flat, and said that it was useless to apply the ointment to an unclean ulcer. He noted that there was little chance of cicatricial contraction under this healing, and showed by microscopic examination that the newly formed skin was the same as the normal skin.

In May, 1908, Kaehler substantiated Schmieden's work and modified his technic. He found good results could also be obtained when scarlet red was used on unhealthy granulating wounds. He healed a varicose ulcer with scarlet red, and then was able to thoroughly clean up this new skin and operate through it for excision of varicose veins, thus showing the stability and quality of the newly formed epithelium. He completely healed defects of similar size, one with grafts and one with scarlet red, in exactly the same time.

Krajca, in September, 1908, described further good results. He was the first to use scarlet red in conjunction with partial Thiersch grafts, and found that the edges of the grafts were stimulated as well as the wound edges. He mentions a number of interesting cases. Some of the ulcers, although of large size, healed in a very short time under this treatment. He found the cutaneous irritation due to the scarlet red to be the exception rather than the rule.

Enderlen, in September, 1908, published very satisfactory results, as did Cernezzi and Hubner, in February, 1909. Wolfrom and Cords in the same month wrote on the successful treatment of ulcers and wounds of the cornea by 5 per cent scarlet red salve. Excellent results were obtained in a case of keratitis neuroparalytica. An old corneal fistula was closed by this means. A more rapid regeneration of the tissues was

noted and sometimes an excess of tissue formation, but this soon flattened.

Sprecher, in March, 1909, reported good results in the treatment of ulcerated lupus vulgaris, ulcers of prepuce, vulva, labia and cervix, varicose leg ulcers, syphilitic ulcers, ulcers of the breast, etc. He did not observe any local irritation or toxic effect in his series.

Rebaudi, in April, 1909, described the use of scarlet red in gynecological conditions and obtained excellent results in the treatment of erosions, tears, etc.

Pleth and Pleth, in May, 1909, detailed the successful use of scarlet red on ulcers of various kinds. Heermann, in June, 1909, reported the success of his treatment with scarlet red of tympanic membrane perforations. He said the duration of the perforation seemingly had no effect on the rapidity of the healing. Suppuration did not appear during this treatment.

Ducros, in July, 1909, reported favorable results on granulating wounds, as did Morawetz, in September of the same year. Hayward wrote in the same month concerning the use of an 8 per cent ointment of amidoazotoluol, which is, as I have mentioned before, a component of the scarlet red used by Fischer. His results on a number of granulating wounds were even more favorable than with the scarlet red, and he felt convinced that this was the stimulating portion of the dyestuff.

It does not seem possible that amidoazotoluol is alone responsible for the epithelial stimulation, as a number of observers, myself included, have noted very favorable results produced by the clinical used of dyestuffs which do not contain amidoazotoluol.

Grossmann, in December, 1909, reported favorable results with scarlet red salve, amidoazotoluol ointment and amidoazotoluol gauze, in the treatment of wounds following operations on the nasal passages, and in perforated tympanic membranes. Halle, and also Levy, said that they had been successful in similar cases with the scarlet red.

Hartman and Beyer stated at the same meeting that they had used scarlet red in a small number of cases without any particular success. Sonntag and Brühl said they had failed to get rapid results in similar cases.

Auerbach, in 1909, published a number of successful results in the treatment of ulcers occurring in skin and venereal diseases, varicose ulcers, etc. He was unsuccessful in only one case, a multiple leg ulcer which was complicated by extensive varices. The other leg of this patient had been previously amputated for leg ulcer. He used the treatment with success on wounds which were discharging copious purulent secretions. He had irritation with 8 per cent scarlet red, so tried 4 per cent, which he found could be used continuously. Dauthuile also reported favorable results.

The papers which have appeared in 1910 are as follows: Rammstedt and Jacobsthal mentioned excellent results in the healing of ulcers due to X-ray burns. Dreifuss reported favorable results in the treatment of granulating wounds. Cords said it was of use in the eye only in clean ulcers of the cornea, especially if there was deep loss of substance.

Pein detailed a number of cases successfully treated with scarlet red, and gave a very interesting table of the measurements, taken from 25 leg ulcers, from the beginning of the treatment to the time of healing.

Strauss published his very favorable results in the treatment of X-ray burns and other ulcers of various kinds. He says he does not value the use of scarlet red for the rapidity of epitheliation alone, which, in some cases, does away with the necessity of Thiersch grafting, but for the solid epithelium which is of great value, especially in the region of the joints. By this healing contractions and scar tensions can be avoided. Stein reported good results in otiatrics. Scharezki was very successful in the treatment of skin defects of various kinds.

Katz reported favorable results with 8 per cent scarlet red and amidoazotoluol. Simin had excellent results following the use of scarlet red.

Nance (J. Ophth., Otol. & Laryngol., 1911, p. 41) reported very favorable results with scarlet red in the treatment of corneal defects.

It can be seen from the above that by the use of scarlet red and amidoazotoluol very satisfactory results have been obtained. The tone of nearly all of these papers has been enthusiastic, and the only unfavorable results are those reported by Hartmann and Beyer, Sonntag and Brühl. All of these were in aural cases.

Since the publication of my paper I have continued to use scarlet red on a number of other cases with almost uniform success, and have little to add to the technic described at that time.

I find marked epithelial stimulation even when the wounds are unhealthy and the discharge is profuse. This has also been the experience of Kaehler and Auerbach, although nearly all the other writers, beginning with Schmieden, have stated that it is useless to apply the scarlet red ointment to any but a perfectly clean granulating wound. Of course the most rapid results are obtained on flat healthy granulating surfaces, but a great deal of progress can be made by its use while the granulations are being brought into this condition.

Strauss objects to the use of scarlet red put up in balsam of Peru ointment, blue ointment, iodoform ointment, etc., as recommended by me, in the treatment of unhealthy granulating wounds, on the ground that the ointment is of no use on such ulcers, but my experience has evidently been very different from his. I consider the use of such combinations to be of value in the treatment of unhealthy granulating wounds, as the scarlet red in itself has no antiseptic qualities, and the cleansing process due to the balsam of Peru, etc., can in this way be carried on while the scarlet red is being used, as well as by the alternating dressing.

Technic.—An outline of the technic will suffice. Cleanse the wound thoroughly with boric or salt solution and dry. Peroxide of hydrogen may be used before the boric solution if the granulations are unhealthy. The free use of a nitrate of

silver stick is advised to keep down exuberant granulations. Tincture of iodine, U. S. P. strength, may follow the silver nitrate or be used on alternating days, and is a powerful and rapid method of cleansing granulations.

The strength of the scarlet red ointment ordinarily used is 8 per cent, and it should be alternated every 24 to 48 hours with some bland ointment. By applying a weaker ointment, say 4 per cent, it can be used over longer periods without danger of the severe irritation which occasionally occurs.

The most satisfactory method of applying the ointment is as follows: Anoint the skin surrounding the defect with some bland ointment up to about one centimeter of the wound edge, as this prevents possible irritation. Then spread the scarlet red ointment in a thin layer on perforated old linen and apply to the wound, either along the edges or over the whole surface. A light dressing of sterile gauze secured by a bandage completes the procedure.

I have applied the scarlet red ointment to a number of wounds and then exposed them to the air and sunlight. The healing is very rapid and the drying out of the surface is most noticeable.

It is safe to use a 4 per cent scarlet red ointment on partial skin grafts of all kinds 48 hours after grafting, and there is rapid stimulation of the wound edges and also of the grafts themselves.

CASE REPORTS.—I will mention only one case to illustrate the efficacy of scarlet red. A very feeble old lady, 84 years old, was badly burned across the shoulders six weeks before she came under my care. During that time she had been carefully treated by her family physician with the usual methods. The wounds had done well for several weeks, and then had become sluggish and no further progress could be made. The patient's general condition was bad on account of a weak heart and chronic nephritis, and was becoming serious under the strain. I was called to consider the advisability of grafting.

There were three ulcers, one over the right scapula, 5 x 10 cm., another over the left scapula, 5 x 8 cm., and a third ulcer 8 x 10 cm. situated in the mid-line between the other two. Those over the scapulæ were covered with clean, but edematous granulations, which had not yet reached the level of the skin. The central wound was still covered, to a large extent, by a slough which was made up of the whole thickness of the skin and some subcutaneous tissue. The epithelial edges of these ulcers were very sluggish.

On account of the condition of the patient and the situation of the wounds, I decided to try scarlet red instead of grafting.

November 26-27, 1910. The wounds were dressed with a balsam of Peru and castor oil mixture, 1 to 3.

November 28. Scarlet red, 8 per cent, was applied, and thereafter every third day, alternating with boric ointment.

December 7. The last of the slough was removed.

December 16. The wound over the left scapula was healed.

December 23. The central wound was healed.

December 25. The wound over the right scapula was healed.

During the treatment the patient was in a critical condition almost continuously and had to be strongly stimulated in order to preserve her life.

The case is instructive from the fact that old age and great debility seem to have little deterrent effect on the stimulating power of scarlet red. The skin edges were stimulated in spite of the presence of a slough in the central wound. It was only necessary to use the scarlet red ointment in nine dressings to complete the healing. The result was a firm, thick and stable skin, which showed no tendency to contract.

After the appearance of Hayward's paper on the efficacy of amidoazotoluol, I had the opportunity of using this substance on a number of granulating wounds of varying etiology. The results have been excellent.

Calculating the amount of amidoazotoluol in scarlet red from the molecular weights, we find that there is 3.76 per

FIG. 1A.

cent of amidoazotoluol in an 8 per cent scarlet red ointment. I have used this strength as well as 8 per cent in simple vaseline, and also in the balsam of Peru and other ointments suggested earlier in the paper. I will illustrate the efficacy of amidoazotoluol by briefly reporting two cases.

CASE I.—A boy, 14 years old, fell into the fire while in an epileptic attack and was severely burned. He was admitted to the hospital and was much improved, during his five months' stay, by grafting and various other methods. He was then sent to the Out-Patient Department for dressing, and as no further progress was made in the healing he was referred to me eight months after the accident.

The size of the unhealed areas at this time can be well made out in the illustrations. The wounds were covered with very exuberant granulations which secreted actively. The epithelial edges were at a standstill. The patient refused to be grafted and it was decided to try eight per cent amidoazotoluol ointment. The granulations were trimmed off with scissors, then cauterized with silver nitrate, and this was followed by tincture of iodin. This

procedure was carried out whenever necessary throughout the treatment.

February 24, 1910 (Fig. 1, a and b). All of the ulcers were dressed with amidoazotoluol ointment and this was alternated every 24 to 48 hours with balsam of Peru and oil, zinc oxide or boric ointment. A stimulation of the epithelial edges was noticeable within 48 hours.

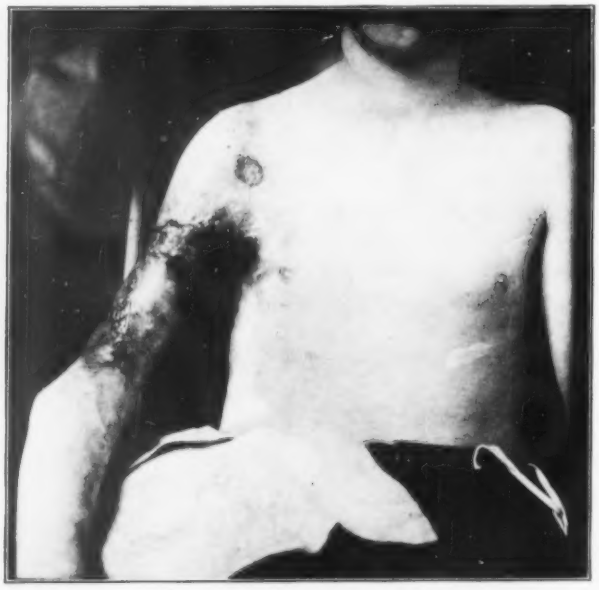


FIG. 1B.

FIG. 1C.

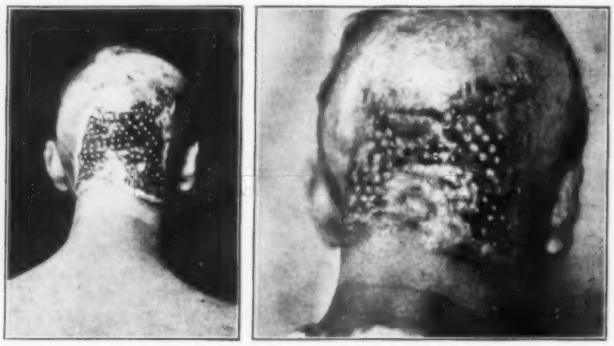
FIG. 1.—CASE I. Sluggish ulcers following burn. Healed with amidoazotoluol. a, b, taken February 24, 1910, eight months after the accident. The ulcers are surrounded by scar tissue. There is partial web formation in the axilla. The exuberant granulations and sluggish wound edges can be well seen. c, taken May 9, 1910. Shows the character of the healing. There is no tendency to contraction. The web formation is less marked.

After the first dressing of the large areas with amidoazotoluol a temporary change of color was noticed in the urine. The patient was dressed at 5 p. m. and the urine voided was as follows: February 24, 6.40 p. m. watery, 500 cc., 9.30 p. m. light lemon, 450 cc.; February 25, 4.30 a. m. *amber*, 430 cc., 7.50 a. m. *reddish brown*, 240 cc., 11 a. m. *reddish brown, slightly darker*, 80 cc., 2.30 p. m. watery, 280 cc., 5.55 p. m. watery, 200 cc., 7.00 p. m. watery, 360 cc. Otherwise the urine was negative. The subsequent dressings did not cause a change in the color of the urine.

May 9. The patient was discharged entirely healed (Fig. 1, c). The healing was firm, thick, and looked like normal skin. Examination of this patient 6 months later showed a firm, movable skin, with normal sensation and no tendency to contraction.

CASE II.—A man, 30 years old, was severly burned by an explosion of oil. He came under my care on May 5, six months after the accident, and one of the unhealed areas is well shown in the figure. This wound had improved for a time and then had become sluggish and apparently no further progress could be made from the epithelial edges. Several unsuccessful graftings had been previously done.

The wound was covered with edematous exuberant granulations which were exquisitely tender. An effort was made to put the granulations in a healthy conditon as soon as possible. Toward the end of this process four per cent amidoazotoluol ointment was used as a dressing and was followed by marked stimulation of the edges.



A. B.

FIG. 2.—CASE II. Sluggish ulcer following burn. Healed with small deep grafts and amidoazotoluol. a, taken May 30, 1910, six months after the accident. The ulcer is surrounded by scar tissue. The small deep grafts applied May 28 have all taken and the wound edges have begun to spread. b, taken June 4, 1910. Shows the very rapid epithelial stimulation from the grafts and wound edges after two dressings with amidoazotoluol. The entire wound is healed with the exception of a few small areas, whose aggregate size is not larger than a ten cent piece.

On account of the tenderness it was decided to graft. The patient refused to allow Thiersch or whole thickness grafts to be cut.

May 28. The granulations being in good condition a number of small deep grafts were taken from the thigh under local anesthesia, and transplanted on the undisturbed granulations. The grafts were dressed with narrow overlapping strips of protective, over which was placed a dry dressing.

May 30. The dressing was changed, and all the grafts were found to have taken (Fig. 2, a).

June 1. The grafts were dressed with four per cent amidoazotoluol on old linen. When the dressing was removed 48 hours later it was noted that the grafts were markedly stimulated. Dressed with boric ointment.

June 4. The entire wound, with the exception of one or two small areas was covered with epithelium (Fig. 2, b).

June 11. The wound was entirely healed with firm resistant epithelium, which required no further dressing. Four applications of amidoazotoluol had been made. The grafts themselves had become much thickened and projected above the surrounding skin like little warts (Fig. 3, a). This condition disappeared and the entire area assumed the normal level (Fig. 3, b).

Examination of this patient eight months later showed a firm, movable skin with normal sensation. There was still some pigmentation around the grafts, but this was less marked than at date of discharge.

COMMENTS.—I was able to compare the rapidity of healing caused by scarlet red and amidoazotoluol. Following an extensive burn there were two granulating wounds of about the same size. One was dressed with 8 per cent scarlet red ointment and the other with 8 per cent amidoazotoluol ointment. The healing in both was rapid, but the wound dressed with amidoazotoluol healed first. The character of the healing was practically the same.

A. B.

FIG. 3.—CASE II. a, taken June 24, 1910. Shows the remarkable thickening of the grafts, which project like little warts above the skin level. b, taken August 9, 1910. The grafts have assumed the level of the surrounding skin. Considerable pigmentation can be seen in the healed area surrounding the grafts.

The age of the patient seems to have little effect on the stimulating power of these ointments. The general health of the patient is most important and in some instances forced feeding, fresh air and tonics must be resorted to.

It is interesting that a number of patients with exquisitely painful ulcers have remarked that there is less discomfort after dressing with these substances that after any other dressing, however bland.

In none of the cases have I noted the slightest irritation of the surrounding skin following the use of amidoazotoluol. Although this dressing can be used continuously without irritation, it is best to apply it for 48 hours and then alternate with some bland ointment for 24 hours.

Dressing with both substances causes excess of secretion for one or two applications, but there is marked drying up of the granulations in a short time.

The use of scarlet red and amidoazotoluol in blue ointment is advantageous in the treatment of syphilitic ulcers, and in addition constitutional treatment should always be employed. In the treatment of second degree burns the ointment can be used immediately after the blisters have been cut away. In third degree burns it is best to wait until the granulations have started.

For a time after healing the newly formed skin has a tendency to be dry and somewhat scaly, but this is easily overcome by the applicaton of olive oil or vaseline.

I have not yet seen a wound break down which was healed by the use of scarlet red or amidoazotoluol, although some of the cases have been under observation for over two years.

A grayish membrane is often seen on the granulations after the application of scarlet red ointment. I have not observed this formation following the use of amidoazotoluol.

Thiersch and Reverdin grafts are sometimes tremendously thickened following early dressings with these substances, but this thickening disappears within a few weeks.

At times it is advantageous to apply either ointment directly to the wound and then expose to the sunlight and air.

Scarlet red and amidoazotoluol gauze is prepared by saturating gauze with a 4 per cent or 8 per cent alcoholic solution of the substances and then allowing it to dry.

The substances can be used as a dusting powder by the addition of 4 per cent to 8 per cent strength, to boric powder. I have also tried the full strength powder on a few wounds without irritation. The effect of the scarlet red and amidoazotoluol used in this way is very rapid drying up of the wound and the formation of a tough scab under which the healing takes place.

A simple and satisfactory method of preparing scarlet red and amidoazotoluol ointment is to rub up the substance with a small amount of almond oil until the mass is smooth, and then mix this mass thoroughly with the base.

Both these ointments can be sterilized without interfering with their stimulating properties.

As a rule there is no toxic effect either from scarlet red or amidoazotoluol. Gurbski reports the only case in which any general toxic effect was noted, as follows:

A child, 11 years old, was severely burned by an explosion of turpentine. The lower two-thirds of the thigh and the entire leg to the ankle were involved. After the granulations had formed Gurbski applied 8 per cent amidoazotoluol ointment. Fifteen hours after the application the patient, who had previously been in very good health, began to complain of headache and dizziness. This was followed by violent vomiting and gastralgia. The pulse rose to 110 and was of low tension. The temperature rose to 102.3° F. There was cyanosis of the lips and albumin in the urine.

The dressing was removed and the patient placed on a milk diet. In a few hours all of these phenomena disappeared. Eight days later amidoazotoluol ointment was again applied and the same symptoms reappeared with the exception of the albuminuria. A third dressing, five days later, caused the same symptoms except that the vomiting was less marked.

During the rest of the treatment he applied the ointment to

only one-fourth of the wound at a time, and the toxic symptoms did not again occur. Rapid healing followed.

Gurbski thinks the poisoning was due to the amido group in the amidoazotoluol.

I have dressed very large granulating areas for some time with these substances without any deleterious effect.

In this connection an observation by Stoeber is of interest. He says that it is not uncommon to have bladder disturbances among the men who work in the manufacturing of dyes. This trouble is principally among the workmen occupied in the manufacture of amido combinations of benzol and naphthalin, or in factories where these products are used. The disease is characterized by cyanosis,, vertigo and weakness, strangury and bloody urine. In addition to the above symptoms, in long continued handling of these dyestuffs, hemorrhages and tumor formations in the bladder are observed. None of these symptoms have been noted following the clinical use of scarlet red or amidoazotoluol, except as noted above.

The consensus of opinion is that there is no danger of producing malignant growths by the clinical use of these substances. My own experience has convinced me of this, and although occasionally there is an overgrowth of epithelium, this soon assumes the level and the appearance of the normal skin.

Some authors have gone so far as to state that by the use of scarlet red and amidoazotoluol the majority of skin grafting can be eliminated. This is too broad a statement, but there is no doubt that wounds can be healed by these compounds which could not otherwise be satisfactorily closed except by grafting.

Scarlet red and amidoazotoluol will not heal every wound, but in the majority of cases, when applied with the proper technic, they will cause epithelial stimulation in the edges of the most sluggish wounds, and give a rapid healing which is stable and resistant, and which has the macroscopic and microscopic appearance of the normal skin. There is no tendency to subsequent contraction, and the skin becomes movable on the underlying tissues in a reasonable time. Any one of these characteristics would make the use of these substances well worth trying.

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ON CERTAIN LIMITATIONS IN INTERPRETING THYROID HISTOLOGY

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Any discussion of the limits of histological variation within which a thyroid gland—whether mammalian, avian, reptilian, amphibian or piscine—may be considered normal is largely of academic interest.

It has long been recognized and frequently emphasized by us that the thyroid tissue is extremely labile—reacting quickly to relatively slight physiological variations in the body metabolism and for this reason may show even daily histological changes within narrow limits. The knowledge of this fact, as applying to the thyroid just as truly as to the blood tissue, has made it unnecessary to write long papers to attempt to define in fixed and exact language the strictly normal thyroid or blood tissues. The thyroid tissue being exceedingly active and well endowed with the power to undergo hypertrophy and hyperplasia, one may observe in any animal group insensible gradations in epithelial hypertrophy and hyperplasia from the smallest amount of thyroid tissue compatible with normal body function (the normal) up to marked degrees of thyroid overgrowth. With such gradations in hypertrophy and hyperplasia it is clear that a histological standard of normal must be, within narrow limits, somewhat arbitrary and this fact explains why different observers have adopted somewhat different standards. It has long been evident that a standard of normal could not be ascertained purely by the histological examination of glands taken at random. In the case of mammals the best way to obtain an accurate conception of the least amount of thyroid tissue compatible with normal body function (the normal) is to give minute doses of iodin to a pregnant bitch throughout the pregnancy and after birth to continue the same with the pups up to the sixth month of extra-uterine life; then examine their thyroids histologically, estimate the iodin contents and the relation of the thyroid weight to the body weight. Even then one may not find all the thyroid follicles containing colloid of uniform staining reactions or the lining epithelium of uniform shape and size. One will find that the variations are slight, considering that the measuring rod is unusually delicate as compared with that of most body tissues.

From our six years' experience with the anatomy, the physiology and the chemistry of the thyroid tissue in all the

classes of animals and their orders from the cyclostomes to man we have adopted the low cuboidal epithelial cell as most nearly conforming with the normal type of thyroid epithelium although this type of gland cell may be depressed to a still lower degree of physiological activity following prolonged iodin administration or in senile states.

The above remarks while drawn particularly from work on the mammalian thyroid have been found to apply as well to the piscine thyroid. Zoological literature contains many excellent descriptions of the histology of the fish thyroid and in them one notes the same variations in anatomical structure that have so long been known for the mammalian thyroid. Our experience with the thyroid of Teleosts (bony fish) comprises a rather extensive acquaintance with 93 species and we have also noticed great differences in the histological appearance of the thyroid epithelium even in fish living wild in the streams, lakes and oceans. It has been ascertained by experiment that the thyroid changes do not take place so rapidly in the fish as in mammals, but the range of histological variation is just as great and the still more recent studies in comparative pathology of the thyroid gland have shown that in artificially reared carnivorous fish (the trout and salmon particularly) the thyroid is capable of relatively as great overgrowth as in any other order of vertebrates. This excessive overgrowth which has thus far been observed only in artificially reared fish has of late created much interest on account of the expressed views of several observers, that it is carcinoma. This conclusion is based on the fact that the thyroid overgrowth presents the histological appearance of invasion of the surrounding structures (bone, muscle, cartilage, etc.). In some recent publications[1] we pointed out that, owing to the absence of any capsule and the normally wide distribution of the thyroid follicles in fish, invasion did not have the same significance as it would have in circumscribed and encapsulated tissues and in tissues less well endowed with the power of hypertrophy and hyperplasia, and that in view of these facts other criteria than histological appearances must be provided before a frank diagnosis of cancer could be made.

In a paper by Gudernatsch[2] he rather infers that we claim the priority for pointing out the fact that the thyroid gland in fishes was not encapsulated. This was not our intention as excellent accounts of the fish thyroid in a great many species are to be found in literature[3] dating back as far as 1844, and for that reason we wished only to emphasize the fact that in a non-encapsulated tissue like the fish thyroid any overgrowth might give the histological appearance of cancer without actually being cancer. Experimental work with this overgrowth has amply justified that assumption.

In this connection we wish also to correct a misquotation that appeared in the above mentioned article as follows: "Thus Marine and Lenhart's statement that the normal follicles invade the bones is not appropriate, etc." We have never made such a statement nor could any one read into our descriptions of the normal fish thyroid such an interpretation without distortion. This author further states "In their paper Fig. 6 demonstrates this fact [that normal follicles do not invade bone] definitely, although it is supposed to show a true invasion." The author has evidently completely missed the point we wished to picture as the legend for this illustration clearly states that it represents the effect of iodin on the marked hyperplasias, i. e., the return or involution of the active and extreme epithelial overgrowth to its colloid or resting state. In this given fish the thyroid tissue had invaded bone, muscle, cartilage and had grown up to and elevated the pharyngeal mucosa. There was also extensive absorption of bone and erosion of cartilage which the microphotograph in question does not picture.

In another instance the author does not grasp the meaning we wish to convey when he says "if all glands, the follicles of which spread out far from the main bulk even into the gill region, are highly hyperplastic, then, according to Marine and Lenhart, the colloid material should be nearly or entirely absent in them. Yet it is present throughout the gland." There are all degrees of active epithelial hyperplasia and as the colloid content (as determined by staining and estimating the iodin content) in general varies inversely with the degree of active hyperplasia there are also all degrees of lessening of the colloid content. Now after extensive hyperplasia has taken place and the thyroid tissue has infiltrated all the surrounding structures including extensions into the gill arches, recovery may take place either spontaneously or from iodin administration, i. e., the active hyperplasia may cease from further growth and the epithelium return to a cuboidal form with the filling up of the follicles with colloid. This recovery implies the return to the colloid or resting state or the nearest normal state that such a thyroid can assume. The distribution of these now colloid follicles is, of course, just as extensive as when these same follicles were in their actively hyperplastic state, i. e., if the follicles have invaded bone, muscle, gill arches, etc., during their actively hyperplastic state they will remain in these locations throughout the life of the fish although the epithelium becomes cuboidal instead of columnar and the colloid content increases to the normal amount. In other words physiological recovery from the condition producing thyroid overgrowth (goitre) does not and cannot entail an absorption and disappearance of the follicles.

Just as there are slight departures from follicular uniformity as regards epithelium and colloid content in the normal thyroid so also in the actively hyperplastic thyroid the follicles show variations in the size of the epithelial cells and in the colloid content relatively more marked than obtains

[1] Johns Hopkins Hosp. Bull. 1910, XXI, 95; J. Exper. Med., 1910, XII, 311; J. Exper. Med., 1911, XIII, 455.

[2] Johns Hopkins Hosp. Bull., 1911, XXII, 152.

[3] Simon, J.: Philos. Trans. Lond., 1844, Pt. 1, 295; Baber, E. C.: Philos. Trans. Lond. 1876, Pt. 2, CLXVI, 557; and *Ibid.*, 1881, Pt. 3, CLXXII, 577; Maurer: Morphol. Jahrb., 1885, XI, 129; Dohrn: Studien, XII, Mitteil. Zool. Stat. Neapel., 1887, VII, 301; Mueller, W.: Jenaische Zeitschr., 1871, VI, 428; Mackenzie: Proc. Canad. Inst., 1884, 134; Thompson, F. D.: Philos. Trans. Lond., 1910, Series B, CCI, 91.

in the normal. These variations are not possible of a definite explanation at present, although it is probable that they are in part dependent upon the blood supply, the lymphatic drainage and perhaps upon other methods of interference with the follicle's nutrition which modifies the cells' activity. Thus it is well known that in secondary hyperplasia (hyperplasia occurring in a colloid gland) the peripheral or subcapsular zone undergoes hyperplasia earlier than the central portion and Ribbert[1] has shown in the experimental regeneration of dogs' thyroids following partial removal that the peripheral zone shows hypertrophic changes earlier than the more centrally placed follicles.

These points are mentioned to show that in any phase of the histology of the thyroid one may place a too literal interpretation on slight variations in this very labile tissue which could not be detected at all in tissues less well endowed with the power of hypertrophy and hyperplasia. It is the general and predominating type of changes throughout the gland and not the accidental condition present in certain follicles that determine the state of the gland so far as functional activity is concerned.

[1] Virchow's Archiv f. path. Anat., 1889, CXVII, 151.

PNEUMOCOCCUS PERITONITIS.

WITH REPORT OF A CASE.

By HARVEY B. STONE, M. D., Baltimore.

Pneumococcus peritonitis, not as a pathological finding, but as a clinical entity, presents a fairly well defined symptom-complex, which should be better known and more generally recognized than is the case at present. Although not one of the exceedingly rare diseases, it is still sufficiently infrequent to deserve reporting. These are the reasons which lead to the presentation of this paper, reinforced by certain features of this particular case which seem of unusual interest.

The facts in the case are as follows:

Patient of Dr. Jeffries Buck, female, 5 years old, white.

Family History.—Not significant.

Past History.—Measles, whooping-cough, chicken-pox, pneumonia two years ago, complicated by acute otitis media. After recovery from pneumonia, the otitis persisted and became chronic with frequent exacerbations of earache and discharge. The last of these flare-ups was on March 26, when the child cried at night with earache, was feverish, and awoke the next morning with considerable discharge from the left ear.

Present Illness.—On the morning of March 30, following an indiscretion in diet of the previous evening, she was seized with sudden severe abdominal pain and vomiting. There was also fever and diarrhœa, the stools being of an exceedingly offensive odor. It should be noted that other members of the family also suffered from somewhat similar gastro-intestinal upsets, but without fever being noted, and with rapid return to normal.

The child did not improve. The fever and the abdominal pain, which was generally distributed, but most acute at the umbilicus, and the diarrhœa persisted, in spite of calomel given to clear up any chemical source of disturbance in the intestinal canal. On March 30, the temperature reached 104.5° F. On March 31, Dr. Buck noted some fullness and tenderness of the abdomen with persistence of the former symptoms and requested a surgical consultation.

Physical Examination.—5 p. m., April 1. Child sleeping. Temperature now 102° F., pulse 120, respiration 30. No visible discharge from either ear. Lips dry and cracked. Tongue coated. Child awakened, but remained notably apathetic and continued so during the illness.

Chest.—Heart clear. Lungs entirely negative.

Abdomen.—Slight symmetrical distention in lower half. Respiratory movements limited to chest and upper abdomen. No visible peristalsis. On palpation, general tenderness all over abdomen, most intense below level of umbilicus, but no difference between the two sides. No particular tenderness over appendix region. No masses felt. It was noted that rigidity was slight, much less than the other findings seemed to justify, and that the patient persistently referred the worst pain to the navel. Slight muscle spasm.

On percussion, no areas of dullness were noted. The liver dullness was pushed up about two fingers' breadth above the costal margin.

Rectal Examination.—Rectum ballooned. Tenderness all over vault of rectum. Pelvic organs felt normal. Vaginal discharge noted, which was later stained and showed Neisser's organisms. In this connection it should be noted that the child slept with an aunt who was known to have pelvic inflammatory disease.

As a result of the examination, there was a very definite impression obtained of some intra-abdominal trouble that might require surgical intervention. The picture was certainly not that of any of the usual lesions, however. Appendicitis, some form of obstruction, pelvic inflammation, and other conditions were considered unlikely, and it was felt that the case was obscure and unusual. As the child's temperature had come down two degrees, and the vomiting had ceased for several hours, and there seemed a general improvement, operation was not urged, but the child was placed in the Hebrew Hospital under observation. During the night, the temperature rose again to 104° F., the vomiting recommenced, tenderness and pain became greater, and the leucocyte count was found to be 18,400. An immediate exploration was decided upon in the morning.

Operation.—Through a right rectus incision the abdomen was opened, and at once thick greenish-yellow pus welled out, which resembled condensed milk quite closely in color and consistency. It was noted that the pus was odorless. A rapid search of the pelvis, the appendix, the gall-bladder, stomach and small bowel was made. No lesion accountable for the infection could be found. Everywhere the same pus, with numerous thick flakes of fibrin was found. The serous surfaces were noted as being much less injected than one would expect with so much free exudate. There was absolutely no walling off or abscess formation, every surface inspected being bathed in free pus. A diagnosis of probable pneumococcus peritonitis was made on the character of the pus and the absence of a definite visceral lesion. Cultures were made and stained slides were sent to the laboratory for examination. Gonococcal peritonitis was considered improbable as the pathological findings at operation all pointed against it. Closure of the abdominal wall, leaving space for free drainage, concluded the operation.

Bacteriological Report.—Pus from the abdomen showed a Gram-positive, encapsulated organism occurring in pairs and short chains; considered pneumococcus. A culture and smears made from the left ear immediately at the conclusion of the operation were negative. No discharge from the ear was visible at this time. A stain was also made from the vaginal discharge which, as noted above, showed Neisser's organisms—biscuit-shaped, intracellular Gram-negative diplococci.

Post-operative Course.—For a short time the patient seemed to rally, but the evening of the day of operation, her temperature rose steadily, she became delirious, and died the next day with all the symptoms of a profound intoxication, the temperature having reached 106.2° F., pulse 170. Post-operative treatment consisted in the same measures adopted for peritonitis in general—the Fowler position, the Murphy rectal saline solution, nothing by mouth, frequent subcutaneous infusions of normal salt solution. No autopsy was secured.

These are the general facts of the case. There are one or two features worthy of comment and a brief survey of the subject as a whole may not be out of place.

In the first place, here is a case of what has undoubtedly in the past been called "primary," "idiopathic" or "cryptogenic" peritonitis. Careful questioning, however, elicited a history of pneumonia two years before, with a complicating otitis media, the persistence of this otitis in the interval, and finally an acute flare-up of considerable intensity a couple of days before the onset of a peritonitis caused by pneumococci. Such a series of incidents is, of course, strongly suggestive. It is to be regretted that efforts to secure bacterial evidence from the ear were unsuccessful.

A second interesting point is the laboratory report of pneumococci from the peritoneum and gonococci from the vaginal discharge. An almost identical case was found reported by Dudgeon and Sargent,[1] who comment on this coincidence with a warning that the finding of specific organisms in the vaginal secretion of such a child does not necessarily mean the existence of a gonorrheal peritonitis. A third fact of note is that this case presents a very typical example of one form of pneumococcic peritonitis, and were such cases not so uncommon the diagnosis would not be extremely difficult before operation. In order to substantiate this statement a summary review of the subject is necessary. No attempt will be made at an exhaustive report of the literature, which is now quite extensive, although the disease is comparatively rare.

The disease was first described by Bozzolo[2] in 1885, as an autopsy finding, and first operated on by Sevestre[3] and Nélaton[4] in 1890. Since then numerous isolated cases have been reported, a number of extensive reviews of the subject have been published, and several theses and monographs written. In 1903 von Brunn[5] collected 57 cases occurring in children and 15 in adults. Jensen[6] published an exhaustive article in the same year. Annand and Bowen[7] in 1906 collected all the cases in children published up to that time, finding 91 under 15 years of age. In the same year von Robbers[8] reviewed the history and literature of the condition. Since 1906, in an extensive but not exhaustive review of the literature, 30 cases have been definitely recognized as pneumococcus peritonitis, while a number of papers have probably dealt with this condition, though unrecognized, under titles such as "Peritonitis without ascertainable cause,"[9] "General purulent peritonitis without obvious cause,"[10] etc.

Pneumococcus peritonitis occurs with marked preponderance in children, and especially in the female sex, between 2 and 14 years of age. Various authorities differ as to the explanation of this incidence of the disease, but all agree as to the facts.

Etiologically, the disease, of course, represents a specific infection of the peritoneum, but much discussion has risen as to the portal of entry. Two groups of cases are usually recognized: the primary or idiopathic, and the secondary, in which the peritonitis is obviously consequent to some pre-existing pneumococcic lesion elsewhere. Of such lesions, pleuro-pneumonic involvements are naturally by far the most common, and next to these, in frequency, is otitis media. The recognition of a "primary" form as a distinct group does not seem logical. It simply means that the portal of entry, instead of being obvious as in a precedent pneumonia, is obscure. The modes of transmission accepted as proved by various writers embrace operative infection, transmission by blood and lymph streams, and direct penetration, with or without perceptible lesion, of the diaphragm and the walls of the gastro-intentinal canal.

Clinically the cases fall into two fairly distinct groups—the encapsulated and the diffuse forms, each of which presents a characteristic picture. The encapsulated form begins with a sudden onset, in a number of cases following an indiscretion in diet, with acute abdominal pain, vomiting and fever. In an overwhelming majority of cases, but not in all, there is diarrhœa generally characterized by the very fetid odor of the stools. The local abdominal signs at this stage and in this form are not very pronounced. The vomiting stops in from 12 hours to a few days. The fever, never very high, persists from 8 to 10 days. The diarrhœa is the last of these early symptoms to cease. After ten days or two weeks, local abdominal disturbances become more pronounced. The pain, which may have stopped, begins again, and instead of being general, becomes localized, nearly always in the hypogastric region. Fullness, gradually but steadily progressing, is noticed. Over this distended area dullness on percussion, fluctuation, and occasionally œdema of the abdominal wall develop. These symptoms, again accompanied by fever, become more pronounced, and unless interrupted by death or operation, a spontaneous rupture nearly always through the umbilicus affords escape for the pus. Three stages may thus be recognized—peritoneal invasion, accumulation of exudate, and spontaneous rupture. The prognosis in this form, which undoubtedly represents a relatively benign infection, is good. Annand and Bowen report 86 per cent recoveries in 45 cases of this type.

In the diffuse form of the disease, the symptoms of onset are the same—sudden abdominal pain, vomiting, diarrhœa, fever—but they are all much more intense than in the local-

izing type of infection. The fever, which is perhaps the most objective sign, is always quite high, often ranging well above 104° F. In these cases the virulence of the infection is much greater than the natural defence of the individual. Death may occur in 24 hours. Where the course of the disease is less abrupt, there is often a brief apparent improvement at the end of about 48 hours. In a short time, however, the symptoms grow more marked, abdominal distention, tenderness, perhaps movable dullness become apparent. In short, the picture of peritonitis develops, with interesting qualifications, rigidity as a rule being far less marked than the other symptoms would seem to justify, and there is diarrhœa instead of constipation. There is a high leucocyte count, very elevated temperature and profound toxæmia. The prognosis is exceedingly grave. No such case has survived unless operated on. Annand and Bowen, in 46 cases, 18 of which were operated on, record only 6 recoveries, 14 per cent.

The pathological findings, aside from the determination of the specific organisms, consist in the character of the exudate. This is, in most instances, thick, creamy, greenish-yellow, and odorless. In a few cases, however, the pus has been described as profuse, thin and of a turbid, dirty brown color. In either form the presence of numerous flakes and deposits of fibrin is characteristic. Several writers have noted that the degree of injection of the peritoneal surfaces seemed slight in proportion to the amount of exudate present.

The treatment of any form would seem to be immediate laparotomy and drainage, for the obvious and time-honored purpose of evacuating pus. There are, however, a few dissenting voices from this opinion. Thus Nobécourt [11] thinks it unwise to operate too early, as in all cases surviving the first few days the infection will localize and then there is less danger, in his opinion, of its being spread by the operator. Manifestly this is simply leaving unaided nature to fight its own battle, and if it wins, doing nothing more than forestalling the spontaneous discharge of the pus. The cases which succumb are not given the best possible chance, by which some of them, at least, would be saved. Naturally the prognosis is better in cases first seen in the stage of localized abscess, but nothing is gained and much may be lost by allowing early cases to wait in hopes that walling off will occur.

To summarize: Pneumococcus peritonitis occurs more often in children than in adults, and more often in female than male children. There are two forms: the encapsulated, which exhibits a first period of invasion, a second period of localized abscess formation, and a third of spontaneous rupture of the abscess; and the diffuse form of general peritonitis rapidly fatal unless operated upon. The symptoms of onset in both forms, varying only in intensity, are abdominal pain, vomiting, fever, and diarrhœa. Rigidity is not characteristic. The treatment is surgical intervention as soon as possible. The prognosis of the diffuse form is very bad; of the localized form, fairly good. The pus is characteristic, and often sufficient for diagnosis from its macroscopic appearance alone.

In conclusion, I wish to express my indebtedness to Dr. Ney, of the Hebrew Hospital, for his kind assistance in placing the hospital records of the case at my disposal.

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AN ANOMALOUS DUCT BELONGING TO THE URINARY TRACT.*

By PAUL G. WOOLLEY, M. D.,
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and
HERBERT A. BROWN, M. D., Cincinnati.
(*From the Laboratories of the Cincinnati Hospital.*)

The specimen we wish to describe is of unusual interest because of its extreme rarity, for, in spite of a somewhat painstaking search of the literature we have found no account of any similar condition. It was found during the post-mortem on a patient in the Cincinnati Hospital (No. 153426) who had been admitted for cutaneous blastomycosis, and who died of the generalized form of that disease.

Because none of the symptoms of the patient could be referred in any way to the condition of the genito-urinary tract we shall omit the history and the report of the autopsy, and confine ourselves to an account of the condition only as it referred to the specimens. We believe that the case has been discussed from the dermatological standpoint by Dr. Ravogli.

The left kidney weighed 200 gms. The capsule stripped with slight difficulty and left a moderately roughened, almost nodular surface. The cut section was rather pale, and the line of demarkation between cortex and medulla was indistinct. The cortex was of about normal thickness. The blood vessels were sclerotic. The right kidney showed the same general appearance. The left adrenal showed a somewhat evident hyperplasia of the medulla. The right adrenal was apparently absent.

* Read before the Cincinnati Society of Medical Research, May 4, 1911.

Extending from the antero-mesial aspect of the upper pole of the right kidney, that is, from the normal site of the right adrenal, appeared a distended, tortuous, saculated tube, which ran parallel with the right ureter which it finally passed to enter the posterior surface of the prostate (Fig. 1). The average diamater of this sac was about 2 cm. In its wider parts it was distended to about 4-5 cm. At its lower end it was rapidly constricted, almost to occlusion. Through the lower end a fine probe could be passed into the posterior urethra at the site of the sinus pocularis. In the immediate vicinity of the prostatic part was a blastomycotic abscess which involved, to a minimal extent, the wall of the duct. The upper part of this distended duct ended in a mass of tissue of about 2 x 1 x 1 cm. in size, which was taken to be the remains of an atrophic adrenal and which later proved to contain only one small area which in anyway resembled adrenal tissue. This mass also contained abscesses. There was no connection whatever between the tube and the kidney, ureter or bladder. The pelvis of the kidney was not dilated. Both testicles were present and had undergone descensus.

In the expectation that sections of the specimen would be of some asistance, bits of tissue were taken from the nodule of tissue at the renal extremity, from the sac at its origin near this renal nodule and from the prostatic portion of the tube. The blocks of tissue taken from the uppermost part included the nodule itself and the kidney so that comparison could be made in the same section.

The sections made from these blocks can, for the purposes of description, be divided into three parts; one, representing the mass of the nodule; a second representing the kidney; and a third, the boundary zone between nodule and kidney.

The tissue of the first part was for the most part well-formed fibrous tissue enclosing large and small cystic spaces, large and small blood vessels, nerves, collections of epithelial cells (columnar, as a rule, occasionally cubical), which seem to represent cross sections of ducts (Fig. 6), and blastomycotic abscesses. The larger cystic spaces were lined with a single row of cuboidal epithelium and filled with a granular albuminous material in which masses of desquamated epithelium, polymorphonuclear leucocytes, giant cells, and blastomyces, were imbedded. The smaller cystic spaces were of two particular forms. One form was lined with one or more rows of cylindrical or high columnar epithelium and filled with desquamated cells, cellular detritus, leucocytes, and extra- and intra-cellular blastomyces; the other was lined with one or more layers—usually a single layer—of cuboidal epithelium and contained a material that resembled thyroid colloid (Fig. 4). Occasionally this colloid showed concentric lines and in some cases it was so changed that it stained with basic dyes and appeared quite similar in appearance to the corpora amylacea of the prostate (Fig. 5). As a rule, however, they were rather more irregular than the ordinary prostatic corpora amylacea, and had a striking resemblance to other similar bodies that are occasionally present in the ovary and other organs. The blood vessels had, as a rule, thickened walls and in the majority of instances showed endothelial prolifieration, even, in some cases, to the point of obliteration. The nerves showed no abnormalities, either in cross or longitudinal sections. No ganglion cells were observed.

The tissue of the second part represented merely a narrow zone of kidney tissue in which there were general changes that taken collectively indicated a chronic diffuse nephritis of moderate severity.

The boundary zone between the two parts already described was composed of fibrous tissue that firmly united the kidney and the nodule. This zone was of some little width, but the line of demarcation was narrow, and was represented by a narrow line of renal capsule. In but a few sections, close to the kidney, and yet separated distinctly from it were small localized masses of tissue, glandular in structure, and quite similar to the tissue that is seen in adrenal and renal adenomas, and in which was no sign of ganglion or chromaffin cells (Figs. 3 and 4).

The general impression given by these sections was that one was dealing with a possible combination of renal, adrenal, and ovarian tissue indifferently arranged. Drs. Knower and Wieman have suggested the occasional resemblance to a Wolffian body.

The sections from the sac itself at the upper and lower ends show that the walls of the sac were composed of fibrous tissue with a minimal number of smooth muscle fibers and were lined with low columnar or cuboidal epithelium (Fig. 7).

There are, under more or less normal circumstances, possibilities of but three openings into the prostatic urethra—two, the openings of the ejaculatory ducts, which were present in this case, and one, the opening of the united Müllerian ducts.

There is also the theoretic possibility that as a result of embryonic developmental variations as suggested by Pohlman the ureter might open into the prostatic urethra. Pohlman says that in changing its position on the Wolffian duct from dorsal to lateral, at which time the ureter comes to open distinct from the Wolffian duct and would naturally open in common with it or into parts developed from its lower end, or "the ureter might open laterally to the Wolffian duct and on a level with it. The opening in this case would be found in the prostatic urethra."

If this be a true explanation, then the mass of tissue above the kidney is the remnant of an atrophic or hypoplastic kidney, or it is the remains of the Wolffian body. In the former case we should be dealing with a unilateral multiplicity of kidneys, each with its ureter, one of which opens into the prostate; in the latter we should have to consider that the duct was the result of persistence of the united Wolffian duct and ureter.

There is the other possibility that in this case we are merely dealing with an abnormal course of a complete ureter without any participation of a Wolffian duct, as occasionally happens in cases with accessory ureters. It is to be noted that in such cases the one of the ureters, usually the one which

FIG. 1.

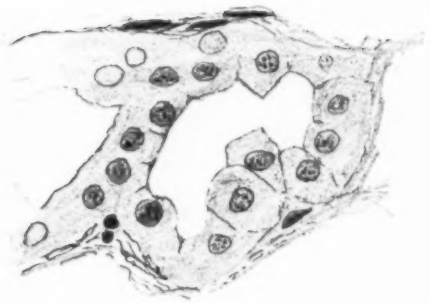

FIG. 3.

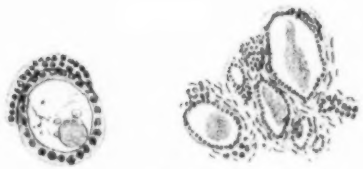

FIG. 4.

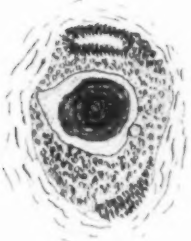

FIG. 5.

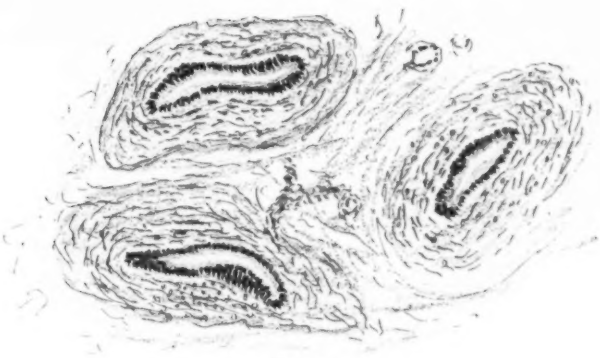

FIG. 6.

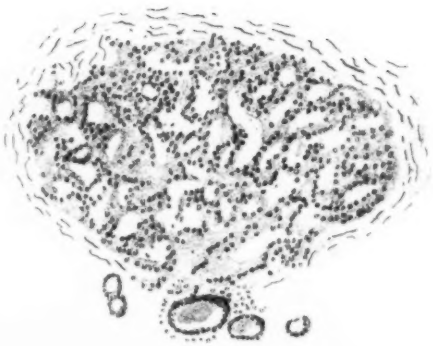

FIG. 2.

FIG. 7.

has the superior origin, lies deeper and may open into the colliculus seminalis, the vas deferens or the seminal vesicle. In any case we cannot account for absence of the adrenal except on the basis of aplasia, or perhaps—if the nodule mentioned above be adrenal—hyperplasia. Either of these results, it might be suggested, may be the result of the development of accessory renal tissue at the expense of adrenal. The embryonic relationships of the urogenital organs are so close that the possibilities of variations are very numerous. Marchand emphasized this from the side of the genito-adrenal organs when he suggested that variations in the sizes of adrenals and ovaries cannot be considered as purely fortuitous.

It is our misfortune that the anatomic evidence at our disposal is not sufficient to permit us to come to any decision as to whether we are dealing with the result of one or the other of the possibilities mentioned.

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ILLUSTRATIONS.

1. A photograph of the gross specimen.
2. The adrenal (?) rest.
3. Same as 2, enlarged.
4. Cystic spaces showing colloid.
5. Cystic space showing corpus amylaceum.
6. Ducts in the nodule above the kidney.
7. Wall of the large duct.

All of the illustrations except 1 and 3 were drawn with a camera lucida at table height using a Leitz ocular IV and obj. 3. Figure 3 was drawn with a Leitz ocular IV and a Spencer 4 mm. A. 0.80 objective.

ACUTE CHOLECYSTITIS WITH LARGE AMOUNTS OF CALCIUM SOAP IN THE GALL-BLADDER.

By JOHN W. CHURCHMAN, M. D.,

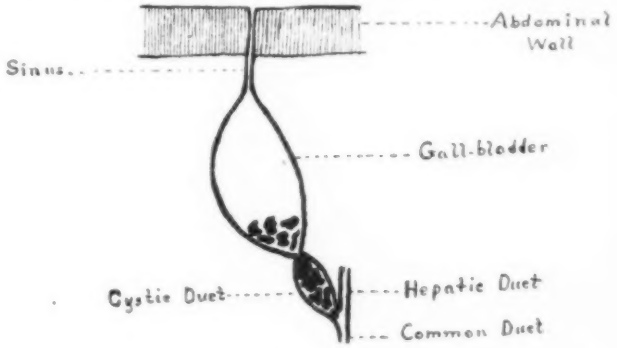
Late Resident Surgeon, The Johns Hopkins Hospital.

In view of the great frequency with which the gall-bladder is drained under conditions identical with those present in the patient whose case is here reported, the absence of any similar case in the clinical literature emphasizes the uniqueness of the observation here made. Moreover—though soaps are found in small amounts in the bile—I have been able to find no reference, in the chemical literature of the subject, to a gall-bladder contents composed almost entirely of soap.

There was nothing unusual about the clinical features of the case. The patient presented the typical picture of an acute cholecystitis. She had never had typhoid fever. The illness began two days before admission with chills, fever, and a general aching. Delirium appeared that night; and the next day there was abdominal pain—at first general, later localized in the right side and radiating to the right shoulder. Nausea and vomiting were present, but there was no jaundice. The physical signs were those of acute cholecystitis. The gall-bladder was not palpable. The liver was slightly enlarged.

At the operation straw-colored fluid was found in the peritoneal cavity, cultures from which remained sterile. The appendix was normal, but the gall-bladder was distended and much inflamed. After isolating it with gauze, it was aspirated; but instead of the pus which was expected a fluid, unlike anything previously seen in the gall-bladder, appeared in the barrel of the syringe. The color of this material but more particularly its strange odor (suggesting a mixture of cod liver oil and turpentine) recalled the contents of a mesenteric cyst operated on a few days previously; and it was for a moment uncertain whether what had been supposed to be gall-bladder might not prove to be a cystic growth of the liver. On opening it, however, a large number of bile-stained stones were found and removed. There was neither bile nor pus in the gall-bladder. The cystic duct was completely blocked by stones. The contents of the distended gall-bladder consisted entirely of a material like that which had been aspirated. The gall-bladder was drained in the usual manner. Convalescence was without event. Three small stones were found in the tube at the first dressing. The discharge from the biliary fistula was at first brownish, later purulent, then thin and mucoid; but it never contained bile.

The wound healed to a pin-point opening, through which



the limpid mucoid material, characteristic of hydrops, continued to drain. The sinus persisted, causing the patient almost no inconvenience, but discharging at intervals. After a year had elapsed, she returned to have it closed. At this operation, the gall-bladder contained much clear mucoid fluid (from which no organism could be grown) and a few facetted, pigmented stones. The distended cystic duct contained many gall-stones and communicated with the gall-bladder by an opening so small that the stones could only with great difficulty be delivered into it. (See diagram.)

The common and hepatic ducts contained no stones. The usual drainage was carried out. Bile appeared in the sinus on the seventh day and soon became profuse. The wound closed promptly and has remained healed.

The strange material removed from the gall-bladder at the first operation was grayish-white in color, glistening, opaque in mass, but slightly translucent in thin layers. It was fluid enough to run into a large aspirator, but its consistency was somewhat that of tooth paste and it could be picked up in mass. It had no property of adhesion whatever, and when handled, failed to come into intimate contact with the skin of the finger, from which it was separated, apparently by a thin layer of oil. None of it stuck to the finger, though its peculiar oily odor remained on the skin. It was ductile and could be pulled out in strands, like pulled candy; but it was somewhat elastic.

An agar slant was inoculated with some of the material and *B. typhosus* grew out in pure culture. The patient's Widal reaction was taken and found positive. It is interesting that cultures made from the gall-bladder at the second operation, one year later, were negative.

A chemical analysis of this material (kindly made by Dr. Slagle) showed it to consist largely of soaps of the calcium salts. Some free fatty acids were also present, but no bile pigments.

There is nothing in the secretion of the gall-bladder proper from which the soaps here present could have originated. This secretion has been carefully analyzed in two cases presenting biliary fistulæ and occluded cystic ducts, and the following composition found.[1]

[1] Birch and Spong: Journal of Physiology. Cambridge. 1887, VIII, 378.

Water and gases		979.7
Solids		20.3
Organic	Mucin Albumin (a trace)	12.09
Inorganic	Chlorine. Carbon dioxide. Sodium (combined with chlorine). Sodium (combined with CO_2). Potassium salts and phosphates.	

These findings agree with other examinations of the gall-bladder secretion.

Hammarsten's analyses of the bile in the liver and in the gall-bladder showed the fats, soaps and fatty acids to be more abundant in the latter situation. His figures are as follows:

COMPOSITION PER 1000 PARTS OF BILE.

The averages of Hammarsten's figures are here given approximately.

	Liver Bile.	Gall-bladder Bile.
Water	About 970	About 835
Solids	" 30	" 165
Mucin and Pigments	" 5	" 42
Taurocholate	" 3	" 23
Bile acids and Alkalis	9+ to 18+	87 to 96
Glycocholate	6+ to 16+	67 to 69
Fatty Acids and Soaps	1+	About 11
Cholesterin	.6 to 1.6	" 9
Lecithin Fat	.2 to 1.5	4 to 7
Soluble Salts	6 to 8	About 3
Insoluble Salts	.2 to .5	" 2

The analyses of other investigators, though the figures have shown some differences from those of Hammarsten, agree as to the substances found and, in an approximate way, as to their relative proportions. All observers have found a small amount of fatty bodies (fatty acids, soaps, fats and lecithin), but none have found them in any such preponderance as was the case in this patient.

NOTES ON NEW BOOKS.

Progressive Medicine, Vol. I, March, 1911. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by HOBART AMORY HARE, M. D. (*Philadelphia and New York: Lea & Febiger, 1911.*)

The most important European and American articles on recent advances and theories in the treatment of the "Surgery of the Head, Neck and Thorax," "Infectious Diseases, including Acute Rheumatism, Croupous Pneumonia, and Influenza," "Diseases of Children," "Rhinology and Laryngology," and "Otology," are reviewed in this volume with the usual care and skill shown by the contributors. This work is of value to any practitioner who wishes to keep himself well informed on the progress of medicine in all its branches—a progress which is steady though sometimes necessarily slow.

A Text-book of General Bacteriology. By EDWIN O. JORDAN, Ph. D. Fully illustrated. Second Edition. Thoroughly Revised. Price, $3.00. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

As errors have been corrected and omissions repaired, which appeared in the first edition of this work, and several new sections added, its real value, to which attention was drawn in our issue of July, 1909, has been increased, and it is fortunate that students have such a useful and reliable book to guide them in their studies.

Accidental Injuries to Workmen, with Reference to Workmen's Compensation Act, 1906. By H. NORMAN BARNETT, F. R. C. S., etc. With Article on Injuries to the Organs of Special Sense, by CECIL E. SHAW, M. D., etc. And Legal Introduction, by THOMAS J. CAMPBELL. Price, $2.50. (*New York: Rebman Company, 1911.*)

This work is more adapted to the use of the English profession than to our own, but since injuries to workmen are as frequent here as elsewhere, and since the question of the proper responsibility in such cases is steadily becoming more acute in this country, and more and more accident cases are being taken into court, it is most satisfactory that American doctors should have such an excellent book to study when they have to deal with "accidental injuries, mechanical and chemical, to the various organs and tissues of the body, including those of special sense." The treatment of such injuries properly finds no place in this work, but diagnosis is fully discussed, and also the remote effects of injuries. This is in fact a text-book to guide physicians how to study an injury which may result in a suit for damages. There

is already a large body of surgeons in this country who will find this book most serviceable, and we are glad to be able to call their attention to it, for the author has handled his material skilfully and written interestingly. The publishers are also to be commended for the quality of the paper which makes the book light and easily held in one hand—so many publications are clumsy and fatiguing to hold.

Surgery of the Brain and Spinal Cord. Based on Personal Experiences. By PROF. FEDOR KRAUSE, M. D. Translated by PROF. HERMAN A. HAUBOLD, M. D. Vol. I. (*New York: Rebman Company, 1909.*)

In his introduction to this work Prof. Krause states that he does not attempt to offer a text book on neurology but "to present numerous ilustrations from nature which are destined to constitute an accurate picture of the status of the surgery of the brain and spinal cord as it stands at this writing." The work therefore does not take up the pathology, pathological physiology, symptomotology, and diagnosis of surgical neurological conditions, but deals with some of the surgical problems relative to these conditions and the surgical procedure used in attacking them which in the author's hands have proven most satisfactory. It is evident from his introduction that Prof. Krause still holds the view that the internist and neurologist should make the diagnoses of surgical neurological conditions for the operating surgeon; a view with which we are not at all in accord.

A book dealing with such a special branch of surgery will have a varying degree of usefulness. To the general surgeon who has had little or no special training in neurological surgery it will be of great aid, for the author has had a large experience in this branch of work and the technic he describes in dealing with various intracranial lesions is superior to that employed by the average general surgeon. To those who intend to devote themselves to neurological surgery the book will be a valuable addition, for the author has appreciated and correctly grasped many of the problems which tend to make neurological surgery a special field of work. To the relatively few who have had considerable experience in the surgery of the brain, this volume will be an interesting exposition of a single operator's technic and experiences in neurological surgery, but will offer little that is especially new.

The first 50 pages of the book are devoted to trephining, the control of hemorrhage from scalp and bone and the method of forming osteoplastic flaps in the approach to lesions in different regions of the brain. It would seem that the method of Von Hardenhain or the plates of Kredel which he employs for the control of hemorrhage from the scalp are unnecessary and time-consuming procedures. A well fitted tourniquet practically always serves the purpose. He describes various methods for controlling hemorrhage from the bone, but admits total inexperience with the most useful of methods, i. e., the use of Horsley's wax. In the formation of osteoplastic flaps he rightly, we think, advocates the use of hand-driven instruments rather than electrically-driven engines. His flaps could be improved upon; a bevelled upper edge made with a Gigli saw prevents the flap from pressing down upon the dura; and if the base of the flap is made narrow and directed downward toward the temporal region it can be fractured and the risk of injury to dura by cutting across it avoided. In agreement with many operators Krause prefers a two stage operation, the first stage ending with the formation of the bone flap. He speaks of the frequency of collapse at the end of the first stage; an occurrence which we have very rarely seen. Collapse at this time must mean undue hemorrhage although Krause states that it often occurs without much loss of blood. While two stage operations are undoubtedly necessary in some instances, we have been accustomed to see the entire operation completed at one sitting; and certainly a one stage procedure is to be preferred if it can be accomplished with no additional risk to the patient.

In exposure of the cerebellum his technic is far from satisfactory. He employs a sitting position which is not only difficult to maintain but is bad for the patient, trying to the anaesthetist and inconsistent with perfect asepsis. Certainly the position used by Cushing is greatly to be preferred. Krause makes use of a unilateral osteoplastic flap which in states of increased pressure must be a difficult and bloody procedure. The exposure of only one cerebellar hemisphere does not allow sufficient dislocation for a complete and satisfactory exploration; indeed, it is only by a wide exposure of both hemispheres tnat a complete exploration of the cerebellum and lateral recesses is possible. Experience teaches that a lesion, such as a cyst, occupying one hemisphere may by pressure cause symptoms entirely referable to the opposite intact lobe; and therefore it is possible that a lesion might escape detection with a unilateral exposure.

His treatment of various lesions of the brain exposed at operation he describes for the most part by citing examples from his series of cases. In the main his treatment is good. He recognizes the necessity of preventing injury to vessels which may cause post-operative cerebral softening, of careful control of hemorrhage and of preventing injury to the pia-arachnoid. It would appear that he drains too frequently. He packs cyst cavities with gauze to obliterate them; we believe that every effort should be made to remove the cyst wall even though thin. He has observed the rapid obliteration of cavities left after removal of tumors or other lesions, but often drains these cavities, which, with careful control of hemorrhage, is unnecessary.

For unlocalizable lesions causing pressure symptoms he does a decompressive operation which is a modification of his osteoplastic flap operation. The objections to it are that the defect is made in a region protected only by scalp; and that it is as extensive, if not more extensive than an osteoplastic flap resection. Compared with this method the simple procedure conducted under the temporal muscle as described by Cushing would seem vastly superior; and we feel that Krause does not at all appreciate the advantages of this method. He does not make use of the method employed by Horsley.

The closure of his wounds is not done with sufficient care, and it would appear that this fact is largely responsible for the number of cases of post-operative fungus or brain prolapse which appear in the volume. Undoubtedly the complication should be less frequent. He does not apparently suture the dural flap made at operation but simply lays it back over the cortex. This seems particularly bad especially if there is increased pressure; for the cortex immediately bulges through the dural defect and adhesions, if not a fungus, result. To conduct a second operation at some future date through a wound closed in this manner would indeed be difficult. The dura must be closed with the greatest care and if any opening is left in it, this should be under some protected region, as under the temporal muscle. Sometimes even the scalp is not sutured but simply held in place with dressings. As previously stated he drains his wounds too frequently; he packs cystic cavities and those left after the extirpation of tumors—procedures which in the presence of increased pressure tend to favor fungus formation.

In all his operations chloroform is used. The operator does not wear gloves. He believes that rapidity of technic, control of hemorrhage and asepsis are the essential factors for success.

As customary in works on brain surgery he devotes many pages (20) to cranio-cerebral topography. He appreciates the difficulty of recognizing the pre- and post-central gyri even when the cortex is exposed; yet he always marks the fisures of Sylvius and Rolando on the scalp the day before operation.

He considers brain puncture and believes it a definite aid in the diagnosis of intracranial lesions. He warns however against the dangers of this procedure. He himself has had several cases of bleeding and in some others an aggravation of symptoms already

present. He mentions the possibility of causing hemorrhage into the ventricle and of encountering a vascular tumor such as an angioma. It would seem pretty definite that this procedure should be used only when the needle can be introduced under direct inspection.

He describes ventricular puncture, giving the various points of election for introducing the needle, but does not take up the indications or contraindications for this procedure. He gives the various methods for accomplishing permanent drainage of the ventricles. As a preliminary to exploration of the cerebellum in cases with extreme tension he does a ventricular puncture which is a very useful procedure.

The translation has been rightly estimated by the translator in his preface. His attempts to follow the German too closely have in many places been made at the expense of good English. The volume is elaborately illustrated with 24 colored plates, some of which are very good, others less well done and showing little detail. The other illustrations are as a whole poor. The print is large and legible with perhaps too frequent use of bold-faced type. The size of the volume is unnecessarily large. In scientific works, with few exceptions, it seems to us a mistake to publish a volume with such broad margins.

The Treatment of Syphilis with Salvarsan. By SANITÄTSRAT DR. WILHELM WECHSELMANN, of Berlin, with an Introduction by PROFESSOR DR. PAUL EHRLICH, of Frankfort-on-Main. Only Authorized Translation by ABR. L. WOLBARST, M. D., of New York Price $5. (*New York and London: Rebman Company. 1911.*)

Wechselmann's experience with the use of salvarsan has been larger than that of any other physician, since he was one of the first chosen by Ehrlich to try the new remedy. In this work Wechselmann gives us the result of his studies of 1400 cases treated, and what he has to say is of importance to all physicians who are using this drug. The profesion at large is now pretty well acquainted with the value, danger, and other characteristics of the medicine, but here we have an as authoritative book on the entire subject as can be had up to the present time. With the lapse of a few years after the discovery of the drug new views may be held in regard to it, but at present this book can but serve as a most valuable guide to all students, for the author has considered all the essential points in regard to the administration of salvarsan. It is well translated and the few illustrations excellent.

Cholera and Its Treatment. By LEONARD ROGERS, M. D., F. R. C. P., F. R. C. S., I. M. S., etc. Price, 4s. (*London: Henry Frowde and Hodder & Stoughton, 1911.*) *Oxford Medical Publications.*

Dr. Rogers has had a large experience with cases of cholera in the Medical College Hospital at Calcutta, and he has written a valuable and interesting work on this disease. The six chapters cover the following ground: I, History of Cholera Epidemics and Their Lesions; II, Epidemiology; III, Etiology and Prophylaxis; IV, Clinical Description; V, Morbid Anatomy and Pathology; VI, Treatment. As in this country few physicians ever have the opportunity to see a case of cholera, this book is not likely to have many readers; but the student of tropical diseases will find it a useful book to have in his library, and will give especial attention to the chapter on Treatment, in which the author sets forth the results of the simple means used by him and by which he has been able to distinctly lower the percentage of mortality in his wards. He advocates the use of infusions of salt solution to lower the concentration of the blood resulting from the frequent evacuations; and also the administration of permanganate of calcium to destroy the toxins produced in the body by the cholera germs. With a combination of these two methods his results have been most favorable, and they deserve to be further tried. The author is modest in his claims as to the value of this treatment, which has at least one great merit, that it seems to do no harm, even if its importance prove less marked with further trial.

Manual of Human Embryology. Edited by FRANZ KEIBEL and FRANKLIN P. MALL. In two volumes. Volume 1 with 423 Illustrations. (*Philadelphia and London: J. B. Lippincott Company, 1910.*)

In the introduction to this volume the editors announce their intention of adhering strictly to human embryology, and of not concealing the gaps which exist in the subject as is sometimes done. They assume rather the very praiseworthy attitude of especially pointing out these deficiencies, as in this way the gaps will be sooner filled.

Comparative embryology is largely excluded and is only introduced in the discussion of the early stages of development.

It is interesting to learn that this treatise on embryology which was projected by His and Keibel has been completed by Keibel and Mall, one of His's most noted pupils.

This is the first manual of human Embryology to be written conjointly by a number of authors, a method which has lately been frequently adopted in other books. Such books are subject to two dangers: first, a lack of unity, and secondly, repetition. These dangers have been avoided here however by very thorough editing and supervision, proved also by the fact that a careful reading of the book has shown a remarkable absence of typographical or other errors. The advantage of a multiple authorship is a greater thoroughness and accuracy of discussion, each author being especially qualified for his task by his own researches.

The reason given for an exclusive human Embryology is the importance of the subject to the physician.

Keibel in his introduction considers the historical development of Embryology, and one is pleased to note that great credit is given to that remarkable genius von Baer and also to His who laid a secure foundation for human Embryology and made possible the great advances of the last 30 years. Keibel calls attention to the spirit of co-operation which is permeating the scientific world, and acknowledges his indebtedness to many investigators. This spirit is part of a broader movement affecting educational institutions which no longer are rivals but rather coadjutors. This volume was published simultaneously in German and English, the English translation being made by McMurrich and the German by Keibel.

Keibel contributes articles on the germ cells, fertilization, segmentation, young ova and embryos up to the formation of the first primitive segment, germ layers and gastrulation and differentiation of external form.

Grosser writes on the egg membranes, placenta and menstruation.

Mall's contribution includes the determination of the age of human embryos and fetuses, the pathology of human ova and the development of the coelom and diaphragm; Pinkus discusses the development of the integument, Bardeen the development of the skeleton and connective tissues, and W. H. Lewis the development of the muscular system.

Keibel's discusion is an excellent one. He accepts Waldeyer's view that at birth or shortly after all oögonia have become oöcytes of the first order and so have before them only further growth and maturation. It is questionable whether the introduction of the term "polocyte" for "polar globule" is desirable. A fuller discussion of sex determination should be given. Keibel's statement that most observers now incline to the belief that sex is always determined in the ovum before fertilization is, in the opinion of the writer, not justified. There is considerable evi-

dence that the spermatozoon has some influence. No mention is made of the work of Morgan and Wilson on accessory chromosomes. Attention is called to the desirability of examining the oviducts in the hope of finding early embryos. Keibel critically reviews the early embryos which have been described and thinks Reichert's ovum has been detrimental to the progress of Embryology because of the wrong impressions created.

In the discussion of the formation of the germ layers he does the reader a service by stating precisely what he means by gastrulation. He defines it broadly as follows: "Gastrulation is the process by which the cells of the metazoan ovum are separated into an upper and lower layer." Attention is called to the gap which exists between Pfannensteil's embryos III and VI of the *Normentafel* of Keibel and Elze. Embryos 3, 4, and 6 of His he considers abnormal.

Grosser gives an excellent account of the method of placentation and explains his classification of placentæ, which is based on the extent of erosion of the decidua. According to his nomenclature the human placenta is a *placenta hæmochorialis discoidalis olliformis*. This is the highest type and is not yet reached by the anthropoid apes. His statement that the endometrium undergoes extensive degeneration in menstruation is, to say the least, misleading. He calls attention to the important fact that the presence of furrows in the endometrium may be indicative of pregnancy and that pathologists, bearing this in mind, may help embryologists to obtain early ova.

In speaking of the increase in size of the uterus in pregnancy, incorrect use is made of the terms Hypertrophy and Hyperplasia.

On page 99 lymph nodes are spoken of as existing in the endometrium; we think this should be "nodule," as lymph node should be used as the equivalent of lymph gland.

Determination of the age of human embryos and fetuses is discussed by Mall with his usual clearness and keen analysis. One is somewhat surprised at the statement, quoting Ravano, that ovulation occurs frequently during pregnancy. He emphasizes the necessity of a standardization of the *corpora lutea* as an aid to the determination of the age of ova, and makes the important suggestion that surgeons might materially assist in this matter by a routine examination of normal ovaries in abdominal sections.

He concludes that the balance of evidence is against the Reichert-His theory and in favor of fertilization occurring near the time of the last menstrual period. The crown-breech and crown-heel measurements are considered the best, corresponding as they do with the sitting and standing height of anthropologists.

In the discussion of the pathology of the human ovum, Mall incorporates largely his studies already published. He has found that 50 per cent of the ova of the first two months received by him are pathological, and considers the causes secondary and environmental rather than germinal. Changes in the chorion are found in a very large percentage of pathological ova, and inflammation of the decidua is regarded as a frequent cause. A classification of pathological ova is explained. He believes with Giacomini that as abortions are frequently due to pathological changes in the ova, threatened abortions should rather be encouraged than prevented, for if retained the embryos may become monsters.

He considers that the evidence from various sources including that of Experimental Teratology indicates that the causes of monstrosities are rather environmental than germinal and calls attention to the importance of treatment of the diseased endometrium in those cases where monsters have been born, to prevent a repetition. His statistics show that seven per cent of all pregnancies result in pathological ova. This discusion is a valuable contribution to our knowledge of the subject.

Mall's article on the development of the diaphragm and cœlom represents in a large measure his own researches in the subject.

The development of the integument is fully discussed by Felix Pinkus. His article includes the consideration of skin pigmentation, dermal ridges and folds, metamerism of the skin, Mongolian spots, hair whorls, the ontogeny and phylogeny of the hair.

He concludes from the evidence, experimental and otherwise, that the melanin is formed *in situ* in the epidermis. The writer does not believe that the evidence is so conclusive on this point as Pinkus represents.

Perhaps the most elaborate and complete article in the book is the one by Bardeen on the development of the skeleton and connective tissues, occupying some 160 pages. It includes a discussion of the histogenesis of the connective tissues, and morphogenesis of the skeletal system including variations and abnormalities in skeletal development. He divides for consideration the development of the cartilage bones into three stages, the blastemal, chondrogenous and osteogenous. This discussion is based largely on his own work and that of Lewis already published. He opposes Rosenberg's theory of the cephalic shifting of the ilium during ontogeny.

The article by W. H. Lewis on the development of the muscular system is an excellent discussion of the subject and is based largely on his own work. The subjects included are the histogenesis of muscle, the segmentation of the mesoderm and the development of muscles in groups and individually. Contrary to the usual view of anatomists he finds no cephalic myotomes but derives the orbital muscles from a mass of mesoderm on the dorsal side of the optic stalk. Also, he fails to find occipital myotomes but believes that the tongue musculature develops from the mesoderm of the floor of the mouth. Futamura's description of the genesis of the face muscles is followed, deriving them from the hyoid arch.

The illustrations in this volume are numerous, but in some cases they are not so good as such an excellent text deserves. A considerable bibliography is appended to the sub-divisions of each article. No index is furnished.

This country is certainly to be congratulated on the excellent showing made by its anatomists, and Mall in particular is to be felicitated on the excellence of the volume. Anatomy in America is greatly indebted to the work, influence and high ideals of Mall. The second volume will be awaited with great interest.

The Medical Annual. A Year Book of Treatment and Practitioners' Index. Twenty-ninth Year. Price 9/6. (*Bristol: John Wright & Sons, Ltd. New York: E. B. Treat & Co., 1911.*)

This is one of the best books in English covering the progress made in all branches of medicine during the past year. The articles are carefully prepared by physicians thoroughly acquainted with the subjects discussed by them. The majority of the contributors are English, but in the list are also the names of two Americans, one Canadian, two Germans, and a Frenchman. The work is supplied with an excellent table of contents, and many good illustrations. It contains also a valuable addition in a list of the principal medical works, and new editions published during 1910, and another of asylums and a trade directory which makes it of especial use to English practitioners; but for other practitioners as well it is an excellent annual.

Puerperal Infection. By ARNOLD W. W. LEA, M. D., F. R. C. S., Lecturer in Obstetrics and Gynæcology, The University, Manchester, England, etc. Price $9. (*London: Henry Frowde and Hodder & Stoughton, 1910.*) *Oxford Medical Publications.*

For a long time German monographs upon practical medical subjects have been available, but similar compilations are only beginning to appear in English. There is particular good fortune in having such an excellent one, as is here given, upon puerperal infection, for this is by far the most important complication with which the obstetrician meets.

The author quotes statistics from the British Registrar General's office, which indicate "that one-half of all the deaths of women occurring in connection with child-birth are referable to infection, while its remote results are a source of ill-health to a much larger number." We are shown that there has been only a slight diminution in the mortality from this disease during the past 40 years, and that in some parts of the United Kingdom there is even a tendency toward an increase. The total puerperal death rate was 5.9 per 1000 from 1851 to 1855; it still amounted to 4.2 per thousand between 1901 and 1906. In England and Wales alone from 3000 to 5000 women die annually from this largely preventable complication. Statistics further indicate that the incidence of infection is very much greater in country districts than in the cities where fairly good conditions would seem to prevail. However, the author regards the whole situation as a grave reproach to our times, and in the prevailing conditions he has found sufficient stimulus to prepare this volume of nearly 400 pages.

The monograph views the subject from every side, and in exhaustiveness compares favorably with the article by Von Herff in Von Winckel's Handbuch. It must prove helpful to those who teach obstetrics, but will perhaps have an even greater value for the practitioner. Fully two-thirds of the book is devoted to clinical matters, and one-half of this section deals altogether with treatment. As might be expected, means of prevention are emphasized as the most important feature in combatting infection, but curative measures are discussed at great length and their relative values carefully weighed. The recommendations made are unusually trustworthy. In the discussion of therapeutic measures about which there is some diversity of opinion, the evidence of different advocates is impartially given, yet the author always frankly commits himself to one view; herein he displays clear reasoning and reaches sound conclusions.

The same judicial qualities are apparent in the first portion of the volume which deals with the bacteriological and pathological phases of puerperal infection. The more recent contributions along these lines have been incorporated, and in many instances first hand information relative to disputed points is given. Thus, from his own investigations the author believes that streptococci may occasionally be found in the vagina during pregnancy. He has also observed that such organisms may possess hæmolytic properties.

The pathology is discussed at length, and the suggestions it affords as to treatment are indicated. The author agrees with those who find in the reaction of the endometrium a very good argument against curetting an infected uterus, for this operation usually does no more than remove nature's defense against the disease.

The one criticism which may be fairly offered pertains to the pathological illustrations: these do not reach the standard justified by the text. The book is a valuable addition to the literature of infection, and will be welcome to those who are practising obstetrics.

Urgent Surgery. By FÉLIX LEJARS. Professeur Agrégé à la Faculté de Médicine de Paris, etc. Translated from the sixth French edition by WILLIAM S. DICKIE, F. R. C. S., etc. Volume II. Illustrated. (*New York: William Wood & Company, 1910.*)

The second volume of this work is divided into four sections, dealing respectively with the genito-urinary organs, the rectum and anus, the strangulated herniæ, and the extremities. Of the first two of these sections it is perhaps sufficient comment to say that they exemplify the excellent characteristics of the work as a whole. That is, the subject is handled concisely and clearly, yet with no tendency to a restriction to simple generalities, as many quite unusual conditions are discussed and typified by case-reports. Logical subdivision of the subject matter into topics and paragraphs, with typographical arrangements to emphasize headings and important conclusions, aids greatly in dispelling the inevitably forbidding effect of page after page of unvarying print, and renders quick consultation of the book easy. The work is further distinguished from the usual uninspired recitation of common places by the numerous ingenious bits of technique and the wealth of striking clinical observations, which give so strong a note of the writer's personalty and add so much to its practical value.

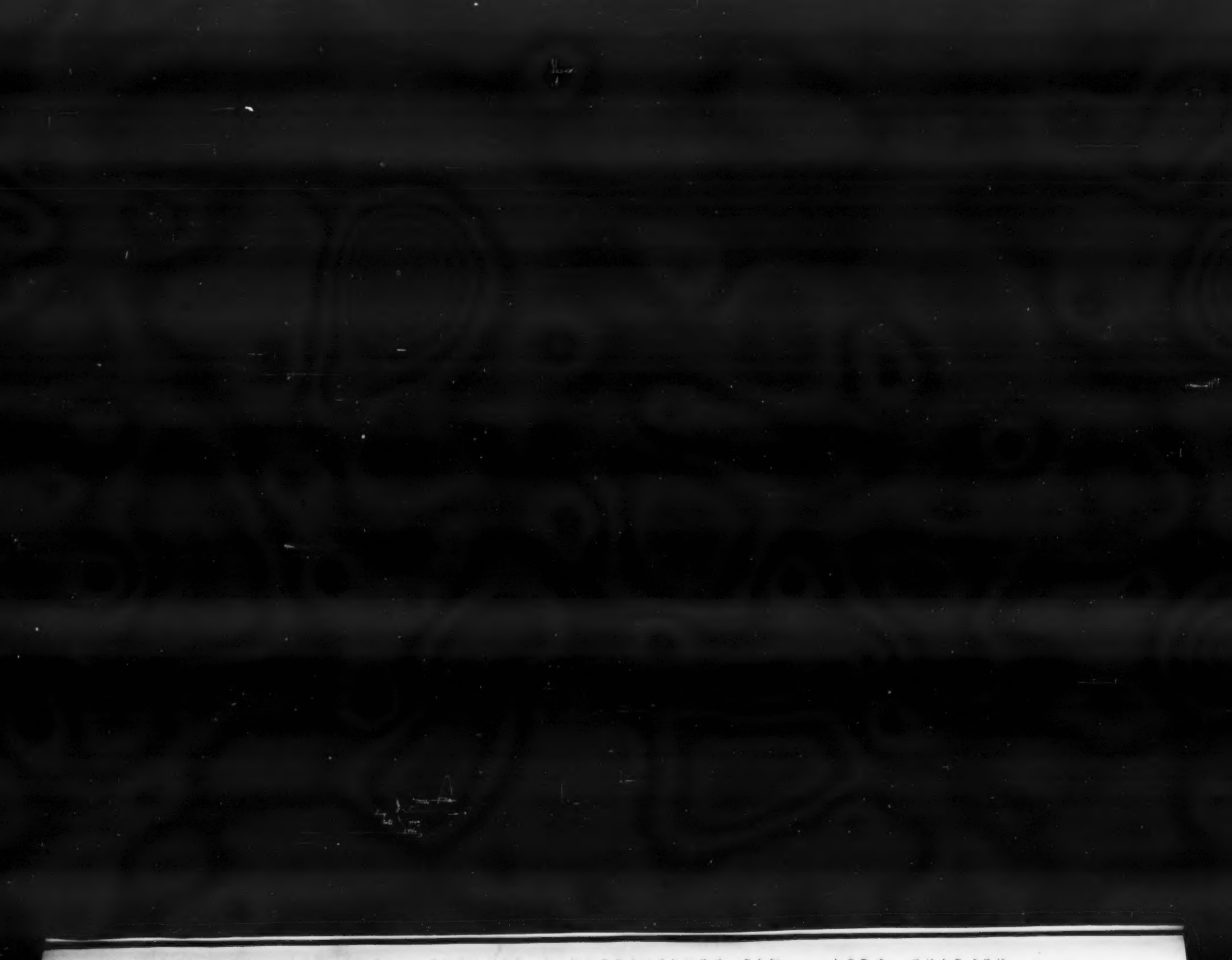
The part of the book devoted to the urgent surgery of hernia demands more consideration than the above remarks, which are true of the work as a whole. This section really constitutes a monograph of authority, and a masterly treatment of emergency hernial surgery. It is the most comprehensive and rational handling of this highly important phase familiar to the reviewer. The unusual types of strangulation are ably discussed, and a perusal of this book makes one feel far less likely to overlook or mistreat some of these quite obscure cases. The last part of the book, dealing with the extremities, is likewise eminently rational and practical. The various subjects are presented with an attitude of healthy conservatism, of the sort that is not deterred from recourse to seemingly radical measures when such measures are in fact truly conservative.

There are certain points that strike one as noteworthy for the shade of difference presented from the familiar American viewpoint. One misses any reference to the so-called Mayo closure of umbilical herniae in a transverse direction. There is a decided fondness displayed for more or less complicated apparatus in the treatment of fractures. The author categorically condemns the use of gauze in packing abscess cavities, using rubber tubes exclusively. A number of conditions are included that many would give no place to in a work on urgent surgery, such for instance as the open treatment of certain fractures. This, however, is purely a matter of degree, since most surgery, excepting plastic and other types of work where an optimum period is awaited, is urgent in the sense that the sooner it is done the better, even when there is no imperative need of haste.

The book is properly and most admirably illustrated, most of the cuts being original. The translator deserves high appreciation for a rendition into English so pure and idiomatic that no flavor of the original French of the text is perceptible.

HARVEY B. STONE.

A Text-Book of Surgical Anatomy. By WILLIAM FRANCIS CAMPBELL, M. D., Professor of Anatomy at the Long Island College Hospital. Second edition revised. Illustrated. Price, $5.00 net. (*Philadelphia and London: W. B. Saunders Company, 1911.*)

In the preface to this edition the author states "that only such additions have been made and errors corrected as to make the text more complete and exact. Several illustrations have been replaced by others which more accurately elucidate the text." The merits of this work were noted by us (Johns Hopkins Hosp. Bull., Feb., 1909), and its success, as shown in the call for a new edition so soon, is a natural consequence of its qualities which make it valuable to students.

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